Vol. 28 SEPTEMBER, 1950 No. 3

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

ALTON OCHSNER, New Orleans OWEN H. WANGENSTEEN, Minneapolis

ASSOCIATE EDITORS

ALFRED BLALOCK, Baltimore I. S. RAVDIN, Philadelphia

Original Communications

Intravascular Agglutination of Erythrocytes (Sludged Blood) and Traumatic Shock. R. O. Heimbecker, M.D., and W. G. Bigelow, M.D., Toronto, Canada ------ 461

Experimental Cardiac Surgery. I. Observation on the Action of a Pump Designed to Shunt the Venous Blood Past the Right Heart Directly Into the Pulmonary Artery. William H. Sewell, Jr., M.D., and William W. L. Glenn, M.D., New Haven, Conn. ---------- 474

Fibrosarcoma of the Soft Tissues of the Extremities. John C. Ivins, M.D., Malcolm B. Dockerty, M.D., and Ralph K. Ghormley, M.D., Rochester, Minn. -- 495

Experimental Evidence of Factors Concerned in the Eventual Recovery of Strangulated Intestine: Effects of Massive Penicillin Therapy. Harold Laufman, M.D., Chicago, Ill. ---------- 509

The Treatment of Staphylococcic Meningitis. Paul Teng, M.D., and Frank L. Meleney, M.D., New York, N. Y. ---------- 516

A Method of Producing Experimental Infected Long Bone Fractures and Their Treatment With Penicillin and Bone Grafting. Allen H. Johnson, M.D., J. Malcolm Edmiston, M.D., H. J. McCorkle, M.D., and Helen Warmer, A.B., San Francisco, Calif. ---------- 534

Esophageal Anastomosis: Types and Methods of Suture. R. W. Postlethwait, M.D., W. Ralph Deaton, Jr., M.D., H. H. Bradshaw, M.D., and R. W. Williams, M.D., Winston-Salem, N. C. ---------- 537

(Contents continued on inside back cover)

Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

Copyright 1950 By The C. V. Mosby Company

SURGERY

ADVISORY COUNCIL

DONALD C. BALFOUR, Rochester, Minn.
VILRAY P. BLAIR, St. Louis
BARNEY BROOKS, Nashville
WILLIAM E. GALLIE, Toronto
EVARTS A. GRAHAM, St. Louis
HOWARD C. NAFFZIGER, San Francisco
HARVEY B. STONE, Baltimore
ALLEN O. WHIPPLE, New York, N. Y.

EDITORIAL BOARD

FREDERICK A. COLLER, Ann Arbor
EDWARD D. CHURCHILL, Boston
VERNON C. DAVID, Chicago
LESTER R. DRAGSTEDT, Chicago
RALPH K. GHORMLEY, Rochester, Minn.
SAMUEL C. HARVEY, New Haven
FRANK HINMAN, San Francisco
EMILE F. HOLMAN, San Francisco
EDWIN P. LEHMAN, University, Va.
FRANK L. MELENEY, New York, N. Y.
JOHN J. MORTON, Rochester, N. Y.
THOMAS G. ORR, Kansas City, Kan.
GEORGE T. PACK, New York, N. Y.
WILDER G. PENFIELD, Montreal
WILLIAM F. RIENHOFF, JR., Baltimore

COMMITTEE ON PUBLICATIONS

Arthur W. Allen
Boston, Mass.

Claude S. Beck
Cleveland, Ohio.

Elexious T. Bell
Minneapolis, Minn.

Isaac A. Bigger
Richmond, Va.

Albert C. Broders
Rochester, Minn.

J. Barrett Brown
St. Louis, Mo.

Alexander Brunschwig
New York, N. Y.

Louis A. Buie
Rochester, Minn.

Warren H. Cole
Chicago, Ill.

C. D. Creevy
Minneapolis, Minn.

George M. Curtis
Columbus, Ohio

M. De Bakey
Houston, Texas

William J. Dieckmann
Chicago, Ill.

Daniel C. Elkin
Atlanta, Ga.

Willis D. Gatch
Indianapolis, Ind.

Charles F. Geschickter
Baltimore, Md.

J. Mason Hundley, Jr.
Baltimore, Md.

Andrew C. Ivy
Chicago, Ill.

Dennis E. Jackson
Cincinnati, Ohio

J. Albert Key
St. Louis, Mo.

Chauncey Leake
Galveston, Texas

Francis E. LeJeune
New Orleans, La.

Harold I. Lillie
Rochester, Minn.

John S. Lundy
Rochester, Minn.

Frank C. Mann
Rochester, Minn.

Charles W. Mayo
Rochester, Minn.

Robert L. Payne
Norfolk, Va.

Leo G. Rigler
Minneapolis, Minn.

Ernest Sachs
New Haven, Conn.

Arthur M. Shipley
Baltimore, Md.

Albert O. Singleton
Galveston, Texas

Maurice B. Visscher
Minneapolis, Minn.

Ralph M. Waters
Madison, Wis.

James C. White
Boston, Mass.

Philip D. Wilson
New York, N. Y.

John A. Wolfer
Chicago, Ill.

Vol. 28, No. 3, September, 1950. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $12.00 a year; Canada and foreign $13.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

SURGERY

VOL. 28 SEPTEMBER, 1950 No. 3

Original Communications

INTRAVASCULAR AGGLUTINATION OF ERYTHROCYTES (SLUDGED BLOOD) AND TRAUMATIC SHOCK

R. O. HEIMBECKER, M.D.,* AND W. G. BIGELOW, M.D.,† TORONTO, CANADA

(From the Faculty of Medicine, University of Toronto)

IN A previous study the relationship between intravascular agglutination of erythrocytes, sedimentation rate, and vascular stasis in trauma was reported.[1] It is difficult to study experimental trauma without introducing a state of traumatic shock and it was soon realized that the character of the blood flow observed in the living vascular bed was being profoundly influenced by the blood pressure and degree of hemoconcentration and vasospasm. Indeed, a slow sludgelike flow could be obtained in sudden traumatic shock with what appeared to be a minimal degree of intravascular agglutination. Knisely had suggested that the circulating agglutinated clumps, which he has described as sludge, might contribute to the development of surgical shock by impeding the circulation and causing a generalized fluid loss. This study was thus devised to assess the role of red cell agglutination in the production of sludgelike flow and to identify its relationship to traumatic shock.

It had previously been concluded that, "Following local trauma to the area under microscopic observation there was cessation of flow in the smaller vessels. The red cells became packed into dark red, homogeneous masses. This phenomenon has been described as vascular stasis. Resolution of stasis was observed in which the columns broke off into the general circulation as circulating clumps. Animals exposed to trauma consistently showed agglutinated clumps of red cells in the general circulation after injury. These clumps appeared to act as emboli, and produced slowing and stasis in areas remote from the trauma."

In this study, three problems were investigated: (1) Can generalized intravascular clumping from trauma occur in the absence of traumatic shock? (2) Is the picture of abnormal flow in the vascular bed in traumatic shock due entirely to the effects of intravascular agglutination? (3) Can a state of clinical shock occur in the absence of generalized intravascular clumping?

Received for publication, Dec. 14, 1949.

*Fellow in Surgery and Physiology, University of Toronto; at present Fellow in Surgery, Johns Hopkins University School of Medicine.

†Department of Surgery and Toronto General Hospital.

METHODS

Microscopic examination of the vascular bed was carried out by 2 principle methods: (1) The area of the external vascular bed chosen for study was the conjunctiva, which was obliquely illuminated by a light source attached to the microscope (Fig. 2). This small focusing lamp was fitted with a heat absorbing filter, and was connected to a transformer and rheostat. Thus

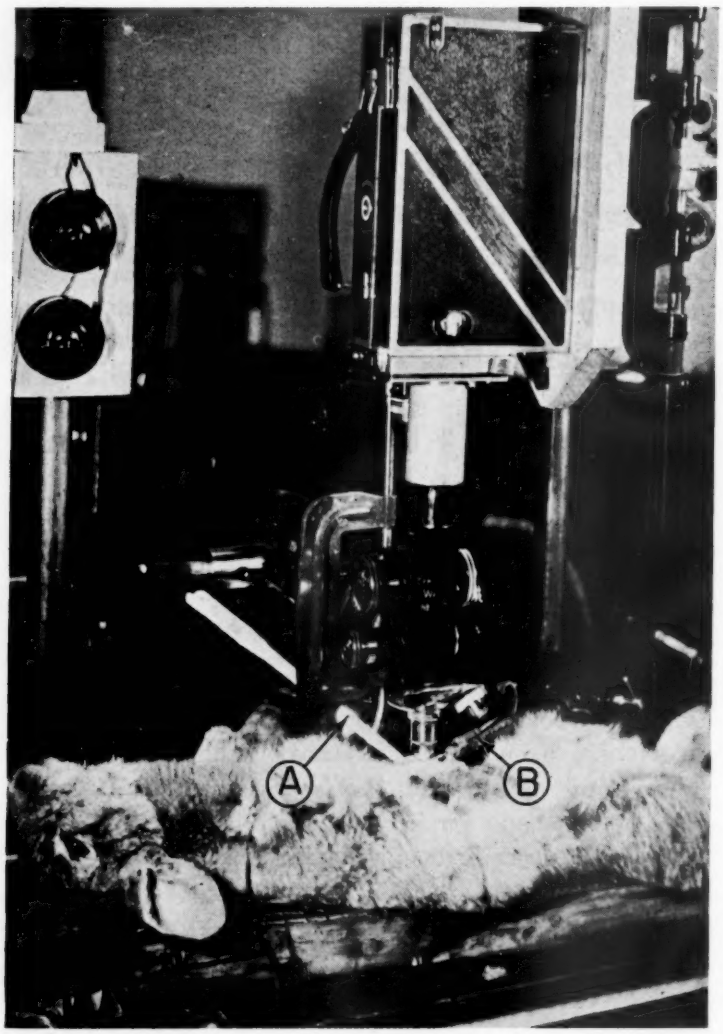


Fig. 1.—Quartz rod transillumination technique. *A*, quartz rod conducting light to tissue; *B*, insulated tube carrying Ringer's solution.

the light could be adjusted to provide sufficient illumination without causing vascular changes due to heat. (2) The area of the internal vascular bed chosen for study was the omentum or mesentery. These tissues were transilluminated by light which was conducted through a fused quartz rod (Fig. 1). Gelatin Ringer's solution at 39° C.[3] flowed constantly over and under the tissue. With this apparatus, as described in detail in a previous communication,[2] it was pos-

sible to keep the same area of the vascular bed in its physiological state, while under constant observation for 4 hours.

Magnifications varied from x7 to x400. A binocular microscope was used for viewing. For cinema recordings a monocular microscope coupled with a Kodak Special movie camera was used. Vessel caliber was determined by a micrometer scale mounted in the microscope ocular.

Rabbits and dogs were used in this study. Only animals free of any clinical evidence of disease were used. All were anesthetized with barbiturates or urethane using light anesthesia so that there would be no depression of cardiac or respiratory function. The conjunctiva was then examined to confirm the presence of an agglutination-free circulation.

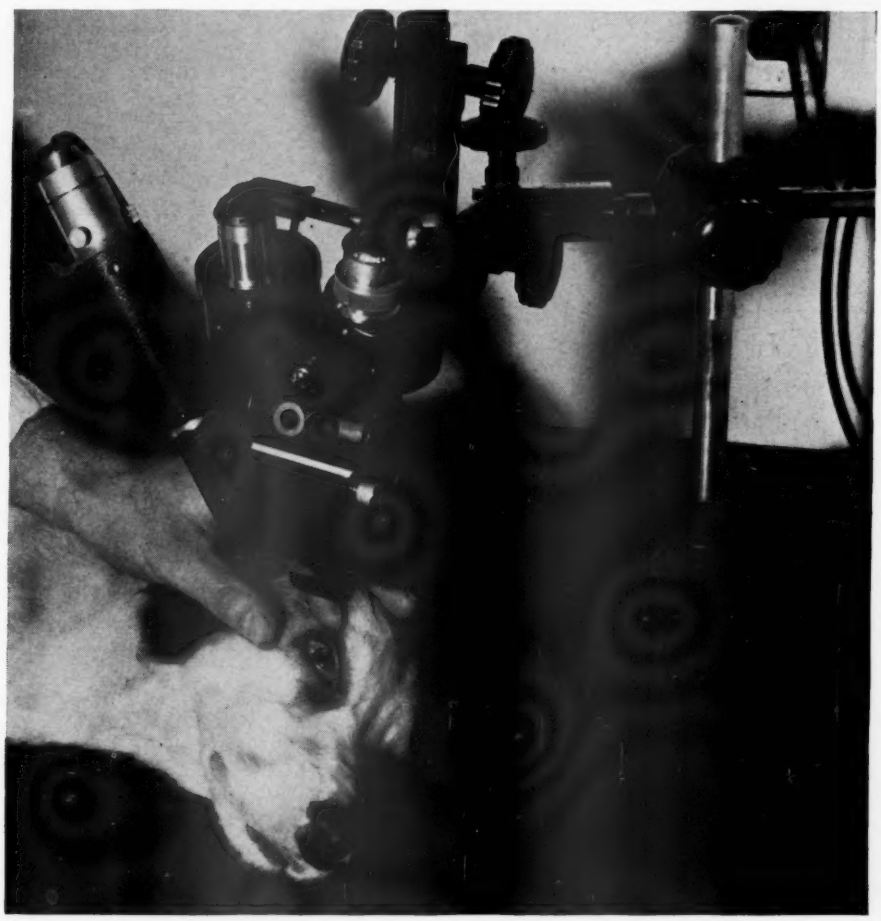


Fig. 2.—Examination of the vascular bed in the scleral conjunctiva by oblique illumination. The steroscopic microscope is on a swing arm mounting. The light source is adjustable, with heat-absorbing lenses.

The development of surgical shock was followed by serial hematocrit readings using Wintrobe tubes. Cardiac rate was recorded along with mean arterial blood pressure, using a carotid canulla and mercury manometer. In more prolonged experiments, systolic blood pressure was determined by a blood pressure cuff and leg plethysmograph.

Trauma without associated traumatic shock was produced in 2 ways: (1) Rabbits were traumatized by 400 to 600 light blows applied to the back legs. A rubber hammer and padded stand were used so that a minimal amount of edema and internal hemorrhage would result. (2) Dogs received 1 second 6 per cent boiling water burns of 1 shaved extremity after the method of Drinker. Their limbs were protected from further injury by a heavy bandage or plaster case loosely applied.

Trauma with mild traumatic shock was produced by 3 second 6 per cent boiling water burns of 1 extremity in the same manner.

Trauma with severe traumatic shock was produced by 10 to 30 second boiling water burns to 6 to 10 per cent surface area of dogs and rabbits. In order to observe and photograph a single area of the vascular bed both before and after the burn, 5 rabbits received flame burns of 1 to 2 minutes. A Bunsen burner flame was applied to their shaved backs while the omental circulation was being observed under the microscope.

A clinical state of shock without trauma was produced in 3 ways:

(1) *Hemoconcentration* was produced by a method of sodium depletion.[4] The dog's peritoneal cavity was carefully infused with a 5 per cent glucose in distilled water solution at 39° C., requiring 100 c.c. per kilogram body weight. If the volume of fluid administered appeared to be causing distress in any way, only part was given at a time, whereupon it was removed before the remainder of the solution was given.

(2) *Hemorrhagic shock* was produced by a graded hemorrhage technique as used by Zweifach and Chambers.[5] The animal was progressively bled over a period of 3 to 4 hours to keep the blood pressure below 70 mm. of mercury.

(3) *Histamine shock* was produced by injections of histamine phosphate of 1.0 mg. per kilogram of body weight.[6]

Intravenous therapy was administered at 25 to 50 c.c. per hour. Citrated fresh dog plasma and reconstituted dried human plasma were equally effective. Also, 0.9 per cent saline solution in distilled water was given.

OBSERVATIONS

Normal Circulation.—This was completely described in the previous communication. Healthy animals showed rapid, even, vascular flow of the cellular elements. Normal rate in the arterioles and venules was indicated by the inability to see individual red cells. In these vessels longitudinal streaking was observed and interpreted as evidence of laminar flow, which is caused by concentric layers of individual cells moving more rapidly near the center of the vessel. A clear layer of plasma occupied the periphery. The smaller capillaries were only 1 cell diameter and allowed the red cells to pass smoothly in single file, demonstrating what Knisely has aptly termed, "a perpetual bottle-neck of the circulatory system."[1] The red cells appeared to remain discrete with no tendency for clumping or rouleau formation.

Intravascular Agglutination Without Shock.—Four dogs were burned, and 12 rabbits were traumatized by light hammer blows (see under Methods). After the injury the animals were active and suffered little or no swelling of the in-

jured limbs. Changes in blood pressure, pulse rate, and hematocrit values were insignificant, showing the absence of surgical shock.

The conjunctiva showed consistent changes, the first abnormality appearing in 12 to 24 hours and reaching a peak in 24 to 48 hours. There was moderately diminished rate of flow, as best seen in capillaries and venules. Most capillaries showed red cells passing in clumps, often separated by clear areas of plasma. Some capillaries were static (cessation of flow) and were usually filled with dark red homogeneous clumps of red cells. Sometimes capillary stasis was only transient, after which the clumps were once again swept into the general circulation. Measurements of vessel caliber showed no definite evidence of arteriolar constriction, although minor degrees may have existed.

The omentum and mesentery showed similar circulating clumps, but rapid flow persisted, and at no time was there any vascular slowing or stasis.

The conjunctival capillary stasis reached a peak in about 48 hours, while the clumping increased until the fifth day, after which it diminished over 10 to 14 days. There was considerable variation in the susceptibility of different animals to red cell agglutination, but all showed some degree of change.

Intravascular Agglutination With Mild Traumatic Shock.—Burns designed to produce mild surgical shock (see under Methods) were administered to the hind legs of 25 dogs. After the injury these dogs appeared lethargic and showed moderate swelling of the burned leg. Blood pressure, pulse, and hematocrit changes are given in Fig. 3. This clinical evidence of shock was usually observed 8 to 10 hours after the burn. No deaths occurred.

Circulatory changes were noted earlier and they were more marked than following trauma without shock.

The conjunctival vessels showed earliest change in flow at 5 to 8 hours, reaching a peak in 24 to 48 hours. As in the previous group of animals, the vascular stasis diminished after 5 days, but the clumps were still evident when last observed on the tenth day. Slowing of the flow was more marked, with many venules showing a creeping, porridgelike flow. Some showed temporary stasis, often followed by a reversal of direction of flow. Many capillaries were permanently static. Others showed clumps rushing through. Vasoconstriction was noted in many arterioles.

The omentum showed similar circulating clumps, but no appreciable vasoconstriction, slowing of flow, or stasis.

Intravascular Agglutination With Severe Traumatic Shock.—Burns designed to produce severe traumatic shock (see under Methods) were administered to the hind legs of 13 rabbits and 20 dogs. Here the onset of shock was early, and the animals either died or were sacrificed within 48 hours.

Changes in blood flow through the conjunctiva were early, and marked by widespread stasis as the shock progressed.

As the vascular stasis progressed and spread to involve adjacent arterioles, they appeared to relax and resume their normal size. Some degree of relaxation of capillaries was observed after they had become static. This is not in keeping with the work of Zweifach, Chambers, and Lowenstein, who stated

that vasodilatation is the primary phenomenon producing pooling and trapping in tourniquet shock.

They also described periodic waves of contraction of arterioles and metarterioles in normal circulation which they have called vasomotion. They have observed an accentuation of vasomotion in early stages of tourniquet shock.[11] We have observed vasomotion in the normal animal but have failed to see an appreciable increase in any stage of burn shock. The precapillary sphincters which they described have not been identified, and their mode of action not visualized.

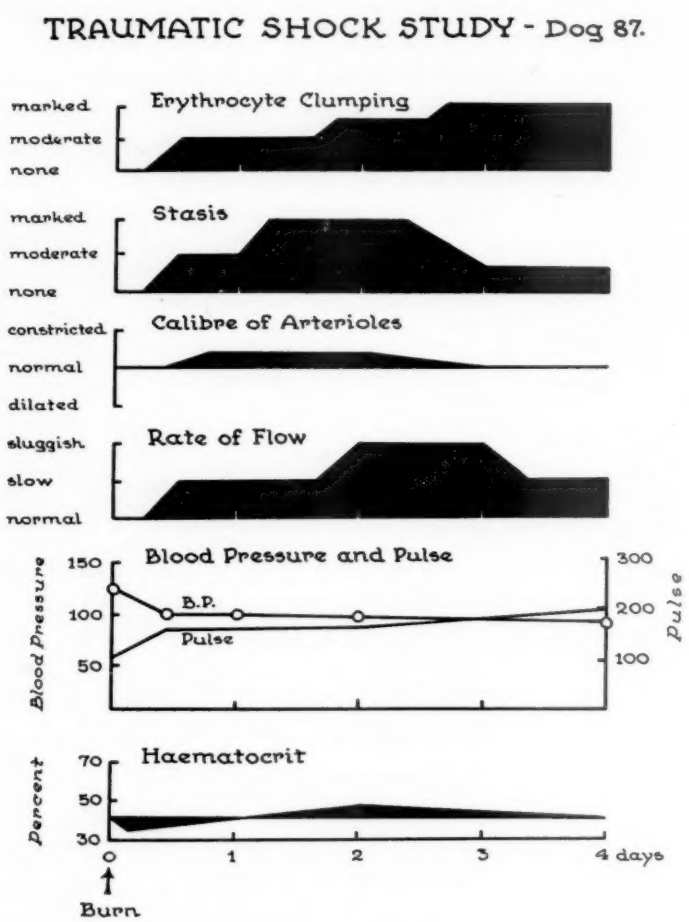


Fig. 3.—The relationship between traumatic shock and intravascular agglutination in a typical experiment.

Intravascular Agglutination With Mild Traumatic Shock, Treated by Intravenous Infusion.—Six experiments were performed on dogs previously described as having mild traumatic shock. Transfusion of plasma and 0.9 per cent saline solution were administered in an attempt to see how much the diminished blood volume of traumatic shock might be contributing to the vascular changes observed. It was hoped that by correcting the low blood pressure,

hemoconcentration, and peripheral vasoconstriction, one might observe the true effects of the agglutinated clumps of red cells upon the vascular bed.

Intravenous infusions were given at various intervals from 24 hours to 7 days following the burns. In every case a definite change occurred in the observed flow through the peripheral vascular bed coincident with the intravenous infusion.

The rate of flow was accelerated so that slow porridgelike flow or reversal of direction of flow no longer remained. There was often an apparent reduction in the degree of peripheral vasoconstriction. Capillary stasis was overcome in many fields observed.

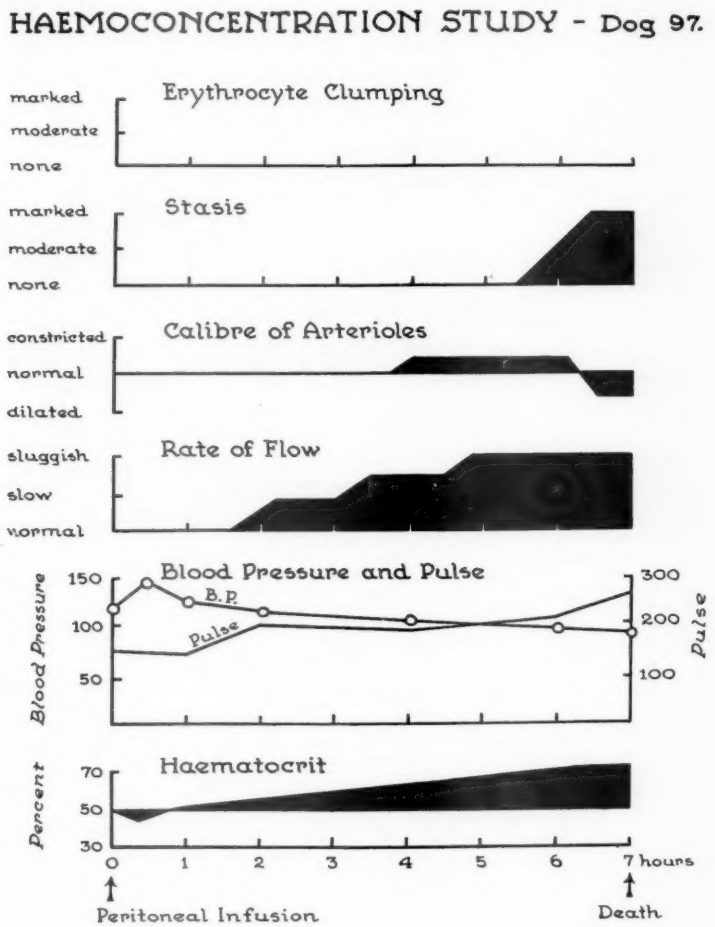


Fig. 4.—Illustrating the absence of intravascular agglutination in shock due to progressive hemoconcentration in a typical experiment.

However, even with relatively large amounts of intravenous therapy, in no instance did the flow return to normal. Circulating clumps, previously camouflaged by the very slow flow, were now readily identified. The rate of flow was accelerated, but the circulation in the smaller vessels was still impeded by the agglutinated clumps. Saline solution and plasma produced simi-

lar effects, but that of plasma was more prolonged. The infusion fluids may have possessed some deagglutinating properties.

Plasma infusions sufficient to approximately restore blood volume produced improved circulation for 4 to 5 hours. Why this improvement did not last longer has not been satisfactorily explained.

The Microscopic Vascular Bed During a State of Clinical Shock Without Trauma in Eleven Experiments.—By choice of techniques designed to produce shock without trauma, an attempt was made to illustrate what effect the main components of shock have on the peripheral circulation.

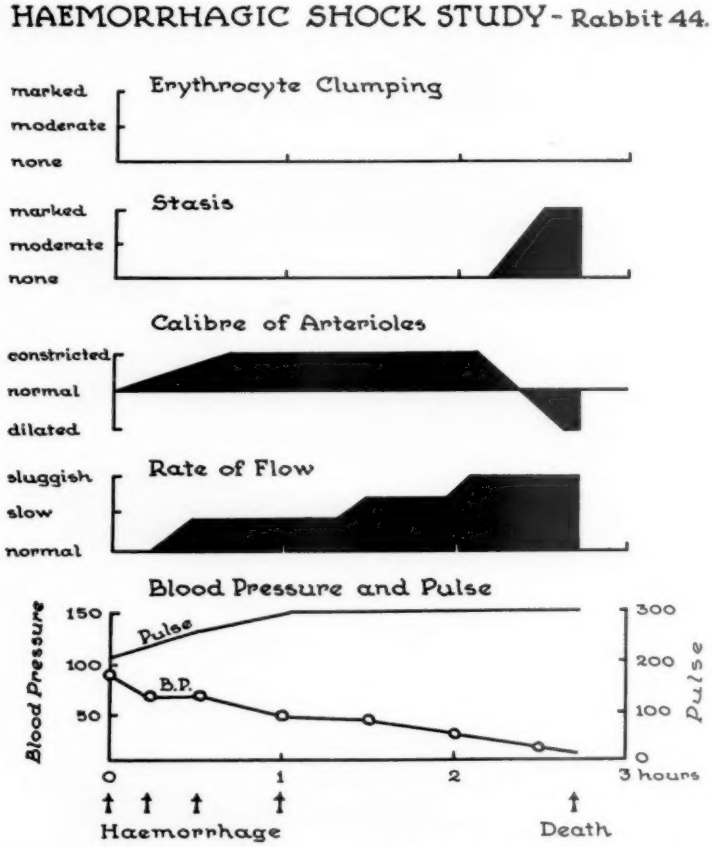


Fig. 5.—Illustrating the absence of intravascular agglutination in hemorrhagic shock in a typical experiment.

Hemoconcentration: To produce hemoconcentration by removal of plasma and injection of red cells would entail techniques which might conceivably produce intravascular agglutination. Thus hemoconcentration with a coincident reduction of blood volume was studied using a large peritoneal infusion of glucose solution.

Three dogs were subjected to a progressive fatal hemoconcentration with no trauma, by a method of intraperitoneal infusion with 5 per cent glucose in distilled water (see under Methods). Blood pressure fall and hematocrit

changes occurred slowly, as shown in Fig. 4. The average hematocrit rise in 5 hours was 47 per cent above the initial reading.

Intermittent observations of the conjunctiva showed a progressive slowing of the circulation as hemoconcentration developed, but no significant stasis occurred until the animal was moribund. Nor was there evidence of red cell agglutination, as judged by the absence of circulating clumps of red cells. The omentum was not consistently examined because it was felt that the peritoneal glucose infusion might upset the normal vascular state.

Hemorrhage: The pure effect of blood volume change with blood pressure fall was studied by graded hemorrhagic shock.

Four rabbits were subjected to a progressive hemorrhagic shock over a period of 2 to 4 hours. The state of shock developed as shown in Fig. 5.

The animal remained under the microscope during the entire experiment and continuous microscopic observations were made on the vascular bed of the omentum. Progressive slowing of the circulation occurred, with marked arteriolar constriction. However there was no vascular stasis or evidence of circulating clumps. Capillaries showed most red cells moving smoothly in single file until death intervened.

Histamine shock: This type of shock was produced on dogs in 4 experiments in order to study a state of low blood pressure without hemorrhage or hemoconcentration. The conjunctiva showed marked slowing of the circulation, with minor degrees of arteriolar dilatation. The extremely slow flow of the cellular elements resulted in cessation of flow in some vessels only if the blood pressure fell very low. As the blood pressure returned to normal, rapid resumption of normal flow occurred in all vessels. At no time was there evidence of circulating clumps which might be expected to contribute to the slowing and cessation of flow.

DISCUSSION

1. Can generalized intravascular clumping occur in the absence of traumatic shock? Yes.

Rabbits and dogs were mildly traumatized by burns and light hammer blows without the production of traumatic shock. Intravascular agglutination of erythrocytes was observed microscopically in all cases. The slow, uneven, vascular flow, which has been described as "sludge" resulted. This appeared to be produced by the circulating agglutinated clumps.

Human cases examined following injury by burns and frostbite have been reported by us.[2] Intravascular agglutination in the absence of shock was observed in the conjunctival vessels of these subjects.

2. Is the picture of abnormal flow (sludge) in the vascular bed in traumatic shock due entirely to the effects of intravascular agglutination? No.

Our early postulation that the pathological flow would be more marked in the presence of traumatic shock has been substantiated by controlled experiments. Moreover, the pathological flow appeared earlier following the injury and was coincident with the development of traumatic shock, as illustrated in Table I.

TABLE I

MICROSCOPIC OBSERVATIONS ON THE CONJUNCTIVAL VASCULAR BED FOLLOWING VARYING DEGREES OF TRAUMA TO ANIMALS' LEGS

TRAUMA (HAMMER BLOWS AND BURNS)	CONJUNCTIVAL VESSELS	
	EARLIEST SLUDGE	SLUDGE IN 12-24 HOURS
No shock	12-24 hours	Slight
Mild shock	5-8 hours	Moderate
Severe shock	½-2 hours	Marked

Plasma infusions were given to the traumatized animals in mild shock to determine whether the more marked pathological flow was due only to possible increased clumping, or to the added factors of shock. With correction of the shocked state there was a noticeable reduction in the degree of pathological flow. The degree of vascular stasis was greatly reduced, and any residual stasis, which often was only slight, appeared to be due entirely to embolic obstruction of the capillaries by circulating clumps.

These experiments illustrated that the presence of sludge or abnormal flow in microscopic vascular bed was dependent on many factors. Agglutinated clumps of red cells themselves might produce the picture of sludge. However, the latter was greatly increased with superimposed shock and its attendant low blood pressure, peripheral vasoconstriction, and hemoconcentration. Others have reported diminished sludge following plasma and saline solution transfusions.[7] Odell and associates[8] reported diminished sludge in eclampsia, following intravenous albumin, but no improvement with plasma or saline solution.

3. Can a state of clinical shock occur in the absence of intravascular clumping? Yes.

By our selection of techniques to produce shock without trauma an attempt was made to illustrate what part the individual components of the shock syndrome play in producing abnormal vascular flow. Clinical shock in the absence of trauma was produced by hemoconcentration, graded hemorrhage, and the injection of histamine. No red cell clumping was observed in any of these shock states (see Figs. 4 and 5). Progressive slowing of the rate of flow occurred, but no vascular stasis appeared until the shock had become very severe.

Should one designate the abnormal flow seen microscopically in these latter experiments as sludge? No intravascular agglutination was observed in these experiments, and yet the flow resembled what has been described as sludge. Knisely, who coined the term "sludge," inferred that the abnormal circulation in trauma was associated with, and to a great extent caused by, the intravascular agglutination of red cells. Thus we feel that the term "sludge" should only be used where such agglutination exists.

To what degree the reduced rate of flow and capillary stasis in traumatic shock is due to red cell clumps is difficult to say. Zweifach and Chambers and co-workers described "pooling and trapping" in the capillaries, and felt that it is due to "an inactivation of the muscular vessels of the bed with a loss of their responsiveness and a disorganization of the peripheral circulation."[9]

They indicated that in tourniquet shock experiments (trauma) the pooling and trapping occurs earlier than in the graded hemorrhage experiments (atraumatic). Could this discrepancy be due to red cell clumping in the former, or is it just due to the increased viscosity of hemoconcentration, or both?

Several authors[10, 11] have described such capillary stasis, stagnation, or pooling, in shock. Gibson and associates, in blood volume studies, reported evidence of "trapping of red cells" within the minute vessels of all organs of the body.[12] Moon, using vital dye, demonstrated generalized fluid loss in experimental traumatic shock.[13]

We have discussed the various factors contributing to generalized change in peripheral circulation in traumatic and burn shock. Erythrocyte agglutination invariably occurs, and appears to be an important factor. Vasoconstriction, lowered hydrostatic pressure, reduced blood volume, and hemoconcentration, all enhance this phenomenon. Pathologically, tissues throughout the body in traumatic shock show minute vessels engorged with red cells, and tissue edema. Our studies lead us to conclude that much of the "engorgement" is in reality complete stasis, which occurs long before death.

On the other hand, generalized vascular changes in hemorrhagic shock were not accompanied by intravascular agglutination of red cells. Slowing occurred, but stasis appeared only as a terminal event, and then only in some minute vessels (see Fig. 4). These observations are correlated pathologically by the absence of vascular engorgement and tissue edema in hemorrhagic shock.

It has been a controversial issue[15] as to whether or not generalized fluid loss occurs in tissues throughout the body in traumatic shock. The development of tissue edema in association with increasing red cell agglutination and stasis remote from the area of trauma has been observed in vivo.[2] This is further confirmed by evidence of tissue edema in pathological sections. This, as Knisely suggested, is probably due to embolic blockage of small vessels by circulating clumps of erythrocytes, producing capillary hypoxia and increased permeability.

It is difficult at this time to assess the amount of generalized fluid loss in the tissues. More investigation will undoubtedly reveal its relative importance in enhancing traumatic shock. At any rate, the vascular stasis seen in some peripheral areas is in effect a pooling and trapping of red cells in these minute vessels. This in turn must reduce the effective circulating blood volume, and consequently contribute to the severity of the shock.

Knisely observed that the degree of sludging was the same in all parts of the vascular tree. We do not concur, in that the degree of sludging in the conjunctiva and nictitating membrane was invariably more marked than that

TABLE II. SLUDGE IN TWELVE TO TWENTY-FOUR HOURS

TRAUMA (HAMMER & BURN)	CONJUNCTIVA				OMENTUM			
	CLUMPING	SLOWING	STASIS	VASOCONSTRICTION	CLUMPING	SLOWING	STASIS	VASOCONSTRICTION
No shock	+	+	+	0	+	0	0	0
Mild shock	+	++	++	+	+	0	0	0
Severe shock	++	+++	+++	+++	++	++	++	++

observed in the omentum and mesentery. The latter showed stasis and vasoconstriction only if the animal were in deep shock following severe trauma, as illustrated in Table II. This supports the evidence that vasoconstriction affects cutaneous vessels much earlier than visceral vessels.[9] The opening up of arteriovenous shunts, once the capillary bed had become blocked, was a consistent response. Mention has already been made[2] of such a mechanism explaining the high oxygen content of venous blood leaving a traumatized limb, as reported by Blalock. In traumatic anuria, the opening up of arteriovenous shunts in the kidney, described by Trueta, is thus not a mechanism peculiar to that organ. Although this study has not been carried out, we feel that the cortical anoxia in conditions related to second nephron nephrosis is probably caused by embolic blockage of cortical vessels by agglutinated clumps of red cells often aided by vasospasm and reduced blood pressure.

SUMMARY

1. Generalized intravascular agglutination of red cells with consequent slowing and stasis occurs following trauma, irrespective of the presence or absence of shock.

2. In the presence of traumatic shock, the microscopic vascular changes or sludging is much more marked.

3. Red cell agglutination contributes to the vascular changes observed. The resulting stasis and edema lowers the effective circulating blood volume, and may be a cause of generalized fluid loss in traumatic shock.

4. Certain forms of clinical shock, such as hemorrhage produced without trauma, are not accompanied by intravascular clumping and do not show the same pathological picture.

5. The degree of change observed in the character of peripheral blood flow in vivo varies in different regions of the body.

CONCLUSIONS

1. The phenomenon of intravascular agglutination of red cells and vascular stasis (sludging of blood) plays an important role in the mechanism of traumatic shock. It offers an explanation for local and generalized fluid loss, as well as for the pathological picture observed in all tissues.

2. In conducting studies of the living vascular bed, one must be careful to recognize that a slow, sludgelike flow can be obtained by hemoconcentration and low blood pressure in the absence of intravascular agglutination.

Acknowledgment.—We wish to thank the Department of Art as Applied to Medicine for the preparation of illustrations.

REFERENCES

1. Knisely, M. H., Eliot, T. S., and Bloch, E. H.: Sludged Blood in Traumatic Shock; Microscopic Observations and Precipitation and Agglutination of Blood Flowing Through Vessels in Crushed Tissues, Arch. Surg. **51**: 220-236, 1945.
2. Bigelow, W. G., Heimbecker, R. O., and Harrison, R. C.: Intravascular Agglutination of Erythrocytes (Sludged Blood), Vascular Stasis, and the Sedimentation Rate of the Blood in Trauma, Arch. Surg. **59**: 667-690, 1949.

3. Chambers, R., and Zweifach, B. W.: Topography and Function of the Mesenteric Capillary Circulation, Am. J. Anat. **75**: 173-205, 1944.
4. Darrow, D. C., and Yannet, H.: Changes in Distribution of Body Water Accompanying Increase and Decrease of Extracellular Electrolyte, J. Clin. Investigation **14**: 266-275, 1935.
5. Zweifach, B. W., Lee, R. E., Hyman, C., and Chambers, R.: The Omental Circulation in Morphinized Dogs Subjected to Graded Hemorrhage, Ann. Surg. **120**: 232-250, 1944.
6. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**: 355-390, 1918.
7. Brooks, F. H., Dragstedt, L. R., Warner, L., and Knisely, M. H.: The Sequence of Circulatory Changes Following Severe Thermal Burns, Abstracts, Amer. Assoc. of Anatomists, Anat. Rec. **100**: 644, 1948.
8. Odell, L. D., Aragon, G. T., and Pottinger, R. E.: Relationship Between Erythrocyte Sedimentation Rate, Sludged Blood, and Plasma Proteins During Pregnancy, Am. J. Obst. & Gynec. **54**: 596-610, 1947.
9. Chambers, R., Zweifach, B. W., and Lowenstein, B. E.: Circulatory Reactions of Rats Traumatized in the Noble-Collip Drum, Am. J. Physiol. **139**: 123-128, 1943.
10. Root, G. T., and Mann, F. C.: An Experimental Study of Shock With Special Reference to its Effect on the Capillary Bed, SURGERY **12**: 861-877, 1942.
11. Chambers, R., Zweifach, B. W., and Lowenstein, B. E.: The Peripheral Circulation During the Tourniquet Shock Syndrome in the Rat, Ann. Surg. **120**: 791-802, 1944.
12. Gibson, J. G., II, Seligman, A. M., Peacock, W. C., Fine, J., Aub, J. C., and Evans, R. D.: The Circulating Red Cell and Plasma Volume and the Distribution of Blood in Large and Minute Vessels in Experimental Shock in Dogs, Measured by Radioactive Isotopes of Iron and Iodine, J. Clin. Investigation **26**: 126-144, 1947.
13. Moon, Virgil H.: Shock, Its Dynamics, Occurrence and Management, Philadelphia, 1942, Lea & Febiger.
14. Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**: 431-440, 1947.
15. Blalock, A.: A Consideration of the Present Status of the Shock Problem: "Problems on Shocks," SURGERY **14**: 487-508, 1943.

EXPERIMENTAL CARDIAC SURGERY

I. Observation on the Action of a Pump Designed To Shunt the Venous Blood Past the Right Heart Directly Into the Pulmonary Artery

William H. Sewell, Jr., M.D.,* and William W. L. Glenn, M.D.†
New Haven, Conn.

(From the Department of Surgery, Yale University School of Medicine)

INTRODUCTION

RECENT rapid strides in the field of vascular surgery are leading inevitably to the point where a direct surgical attack upon the open heart is possible. Obviously, to carry out a surgical procedure on the open heart, some means must be provided for oxygenating and circulating the blood.

The clinical use of any type of artificial heart must, of course, be preceded by an extensive trial with the apparatus in the experimental laboratory. Until part or all of the chambers of the heart can be rendered bloodless, there will be no satisfactory way of reproducing many of the valvular, or combination septal and valvular, lesions seen in the human patient. When such lesions can be reproduced, physiologic observations can be made and techniques for the correction of these lesions can be tested and improved.

It is not yet known whether it will be technically possible to have the venous blood oxygenated by the patient's own lungs or whether some means of extracorporal oxygenation of the blood will be necessary. The extracorporal oxygenation of blood is a major project, although Gibbon,[1, 2, 3] Björk,[4] Crafoord,[5] Jongbloed,[6, 7, 8] Karlson and Dennis and associates,[9, 10, 11] and others have done much to simplify the numerous problems involved. The purpose of this study is twofold; first, to describe a perfusion pump capable of performing the mechanical function of one side of the heart, and, second, to discuss experiments in which this pump was used to shunt the entire vena caval return around the right heart directly into the pulmonary artery.

Many perfusion pumps have been described in the past. The mechanical principle employed in most of these pumps involves the displacement of the perfusate from a "pumping chamber" by compression with a solid, a liquid, or a gas. The cycle is completed by the removal of the compression and the refilling of the pumping chamber by suction or gravity.

Jacobj,[12] in 1895, used a rubber bulb for the pumping chamber and propelled the perfusate by compressing the bulb between two boards. Embly,[13] in 1905, used a somewhat similar arrangement. Brodie,[14] in 1903, Hooker,[15] in 1910, and Richards and Drinker,[16] in 1915, used a piston that moved back and forth in a cylinder. Dixon,[17] in 1922, used a piston constructed from a hypodermic syringe. De Bakey,[18] in 1934, used metal rollers, operated either man-

Aided by a grant from the James Hudson Brown Memorial Fund of the Yale University School of Medicine.

Presented at the Forum on Fundamental Surgical Problems, American College of Surgeons, Chicago, Ill., Oct. 17, 1949.

Received for publication, Feb. 8, 1950.

*James Hudson Brown Junior Fellow.

†Assistant Professor of Surgery.

ually or mechanically, that massaged rubber tubing containing the perfusate and propelled the perfusate forward. A similar pump had been described by Van Allen,[19] in 1932. This type of pump has been used by Gibbon.[2, 3] A system of water under pressure which compressed, in a rigid chamber, an enclosed flexible tube containing the perfusate was used by Dale and Schuster,[20] in 1928, Gibbs,[21, 22] in 1930 and 1933, and Tainter,[23] in 1932. Gas under pressure, compressing and displacing in the same way as the water, was used by Jacobj,[24] in 1890, by Lindbergh,[25] in 1935, by Gibbon,[1] in 1937, and by Björk,[4] in 1948. Barcroft,[26] in 1933 propelled the perfusate with an electrically driven rotary pump.

Some of the aforementioned pumps have been used to take over the function of one or both sides of the heart. The problem of oxygenating the blood in these experiments has been solved in two ways; either the blood was made to pass through the lungs, the animal's own[21-23, 27, 29] or those of another animal,[12, 24] or through a mechanical oxygenator.[1-8, 16, 28, 29]

Several types of valves have been used in these pumps. Gibbs[21] used a circular section of rubber from an inner tube as a flap over the end of the blood-carrying tube. A tag of rubber attached to the circular section was fastened to the side of the tube. He used "chorda tendineae" obtained from a golf ball to hold the flaps in place. Other types of valves have been a solid rubber ball,[22] a rubber stopper with one end partially cut off and a hole bored through the remainder of the stopper,[1] a wide rubber band fastened at each end over the obliquely-cut end of the blood-carrying tube,[4, 5] and still other types.

The flow through the pumps previously described has been determined in a variety of ways. One of the earliest methods was described by Embly,[13] who caused some of the flow to drip on a goosefeather attached to a kymograph. In many of the pumps just referred to, the total outflow was interrupted for a given time and the collected volume was measured. Another method was the redirection of the total outflow into one container of known size, at the same time displacing an equal volume of blood or fluid into the circulation from another similar container.[31] Other investigators[21, 22, 23] have used pumps with a constant stroke volume.

METHODS

Construction of the Pump

The pump consists of a reinforced segment of Penrose tubing enclosed in a glass cylinder. At either end of the cylinder the Penrose tubing is stretched back over the outside of the glass. Two No. 5 rubber stoppers with holes bored through their centers are inserted into either end of the cylinder inside the Penrose tubing, firmly compressing the tubing against the inner wall of the glass. Glass tubes forming the inflow and outflow tracts to the inside of the Penrose tubing, the pumping chamber, pass through the holes in the rubber stoppers. Flap-type rubber valves attached to the inflow and outflow tubes control the direction of flow. Compressed air and suction are delivered alternately through a side arm to the inside of the cylinder (Fig. 1).

The Glass Cylinder.—The glass cylinder is constructed from a piece of glass tubing 15 cm. in length. This tubing has an external diameter of 2.8 cm. and a wall thickness of 0.1 cm. A glass side arm approximately 4 cm. in length and 0.5 cm. in diameter is attached at right angles to the cylinder.

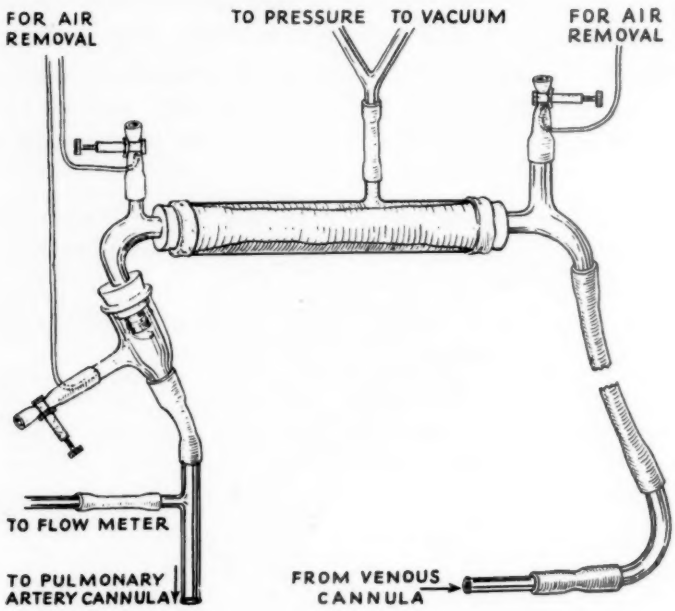


Fig. 1.—Illustration of the pump.

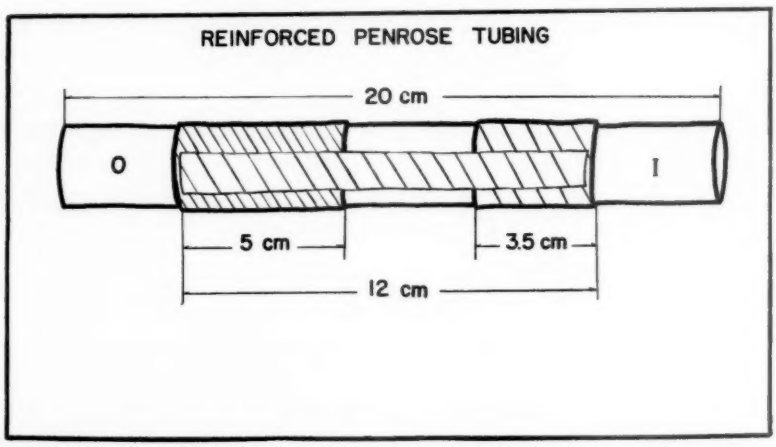


Fig. 2.—Penrose tubing. *I* is the inflow end of tubing. Observe that the reinforcement of this end of the tubing is less than at the outflow, *O*, end of the tubing.

The Penrose Tubing.—Penrose tubing was selected for use principally because of its great flexibility. Experience has shown, however, that the thin wall of a single thickness of Penrose tubing may split where it is compressed by the stoppers. Therefore, two additional lengths of Penrose tubing are slipped over the first. It is also necessary to reinforce the inner segment of tubing to prevent its bulging into the inflow and outflow tubes during the positive pressure phase of the pump. Thicker walled rubber tubing of the desired

dimensions and flexibility would probably not require reinforcement. Such tubing has been developed and is being tested at the present time.*

As used in the experiments described in this paper, a segment of Penrose tubing 20 cm. in length and 2.2 cm. in diameter is reinforced with strips of adhesive tape as shown in Fig. 2. It will be observed that the adhesive tape is applied only to the 12 cm. mid-portion of the rubber tubing. Heavier reinforcement is made at one end of this mid-portion than at the other. The more heavily reinforced end is to be placed at the outflow end of the glass cylinder, which for convenience of description will be referred to as the outflow end of the Penrose tubing. A double thickness of adhesive tape 5 cm. wide is carefully applied around the Penrose tubing at this point. A single thickness 3.5 cm. wide is applied at the opposite or inflow end of the mid-portion of the Penrose tubing. The lighter reinforcement at the inflow end is to encourage this end of the Penrose tubing to collapse first and push the fluid toward the more heavily reinforced outflow end. Further reinforcement of the Penrose tubing is supplied by two single-thickness 1 cm. strips of adhesive tape placed opposite one another between the two encircling bands of tape. When reinforcement of this single-thickness Penrose tubing is complete the two additional segments of Penrose tubing, of equal diameter and length but not reinforced with adhesive tape, are slipped over the first.

The Inflow and Outflow Tubes.—The inflow and outflow tubes to the pumping chamber are constructed from two glass tubes 10 and 12 cm. in length, respectively. Both have an external diameter of 1 cm. and a wall thickness of 0.1 cm. Each tube is bent at its mid-portion to an approximate right angle near which point a glass side arm is attached. Short rubber connections which are clamped off are attached to the side arms, and lengths of polyethylene tubing of 0.038 inch external diameter are inserted into the side arms through puncture holes in the rubber connection for the purpose of removing bubbles of air during the initial filling of the pump with fluid.

The inflow and outflow tubes are each inserted through a hole made in the center of a No. 5 rubber stopper. The rubber stoppers are then inserted firmly into either end of the glass cylinder. The prepared Penrose tubing is not placed in the glass cylinder at this time. When the rubber stoppers are firmly inserted into the glass cylinder with the inflow and outflow tubes in place, part of the smaller end of the rubber stopper does not make contact with the inner wall of the glass cylinder. The stoppers are then removed and the part of the rubber stopper that did not make contact with the glass is cut off. The inflow tube is adjusted in the rubber stopper so that it will extend 1 cm. beyond the cut end of the stopper into the pumping chamber proper. The inflow valve will be attached to this end of the inflow tube. The end of the outflow tube that is inside the cylinder is then made flush with the end of the cut rubber stopper through which it passes.

The Valves.—The valves are cut from the two opposing rubber flaps of a toy noisemaker manufactured under the name of "Razzer" or "Raspberry."

*This tubing has been generously supplied us by the Davol Rubber Company, Providence, R. I.

A circular section of rubber just large enough to overlap the edges of the end of the inflow and outflow tubes is cut from one of the flaps of rubber, and a tongue of rubber is cut from the attached opposed flap of rubber. Two such valves are cut, one for the inflow tube and one for the outflow tube. The valves are attached to the two tubes as shown in Figs. 3 and 4. It will be observed in Fig. 3 that the valve on the inflow tube is protected by a smaller inner glass cylinder which is 2 cm. in length and 1.9 cm. in external diameter. This cylinder is fitted to a narrow collar of rubber on the inflow tube.

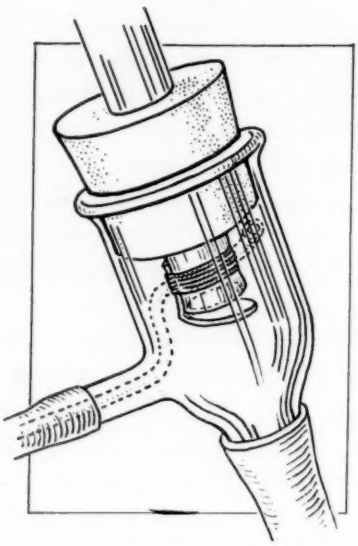


Fig. 3.

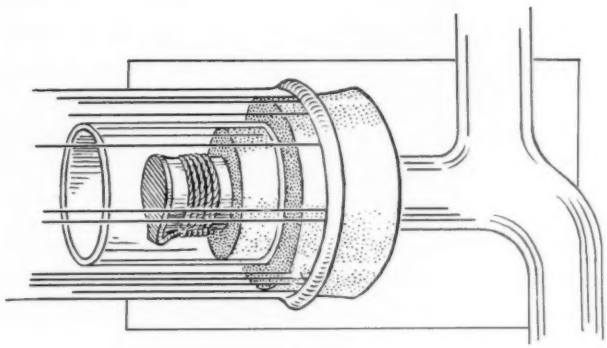


Fig. 4.

Fig. 3.—Outflow tube and valve. The small polyethylene tube can be seen entering through the side arm. The end of it is placed just above the valve to remove bubbles that may collect here during the initial filling of the pump.

Fig. 4.—Inflow tube and valve. Observe that the action of the valve is protected by a small glass cylinder as it lies inside the pumping chamber.

The outflow valve is attached to the end of the outflow tube outside the pumping chamber (Fig. 3). The outflow tube is attached to a larger, funnel-shaped glass tube, 3 cm. in length and 1.8 cm. at its largest diameter, by means of a rubber stopper through which passes the end of the outflow tube. The end of the outflow tube projects beyond this rubber stopper into the larger glass tube below. The valve on the outflow tube is attached as shown in Fig. 4. A glass side arm is attached to the larger glass tube and a polyethylene tube, for the removal of air, is threaded into this segment through a rubber connection.

The Cannulae.—Special cannulae have been made for the purpose of removing the venous blood from the cavae and conducting it into the pulmonary artery. The venous cannula consists of a single length of polyethylene tubing long enough to reach from the right side of the neck of the animal to a place just above the diaphragm. Tubing with an internal diameter of 0.208 inch and an external diameter of 0.260 inch has been found satisfactory for the veins of dogs weighing 15 to 25 kg. For smaller dogs weighing 8 to 15 kg., tubing

with an internal diameter of 0.157 inch and an external diameter of 0.235 inch is used. The cannula is inserted through an opening made in the right external jugular vein and is directed downward through the superior vena cava and the right auricle into the thoracic portion of the inferior vena cava. Prior to the insertion of the cannula, a gentle bend is made in that segment of the cannula which will lie in the superior vena cava. Four or five holes, each ap-

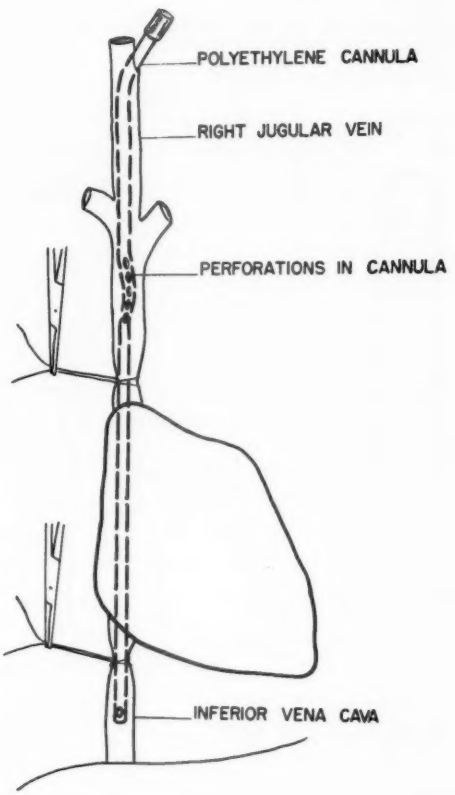


Fig. 5.

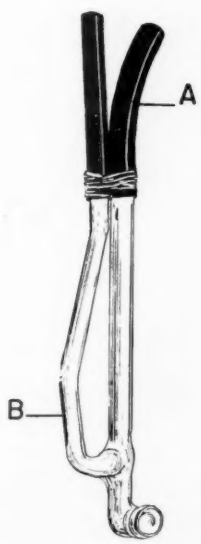


Fig. 6.

Fig. 5.—The polyethylene venous cannula. During operation of the pump double loops of heavy silk thread on the superior and inferior vena cava are drawn tight around the veins, compressing their inner walls against the outside of the polyethylene tubing, preventing the caval blood from reaching the right heart.

Fig. 6.—The pulmonary artery cannula. A and B respectively are connected to the outflow tube and the flow meter. See Fig. 7.

proximately 3 to 5 mm. in diameter, are made in the concavity of the wall at the bend. Several additional holes of the same size are made in the side wall near the end of the cannula which will lie in the inferior vena cava. There are no holes in that portion of the cannula which passes through the right auricle. Moderately heavy silk thread is passed twice around the cavae and the enclosed cannula just above and below the right auricle. While the pump is in operation these ties are pulled taut so as to prevent caval blood from reaching the right heart. The entire venous return from both cavae flows through this cannula (Fig. 5).

The cannula for the pulmonary artery is made of glass (Fig. 6). We have used Pyrex glass with an external diameter of 0.7 cm. and a wall thickness of

0.05 cm. A side arm is attached near the mouth of the cannula for the purpose of measuring flow and pulmonary artery pressure. The flow meter will be described in detail later.

All glass and rubber parts which come in contact with the blood are coated with silicone (General Electric Dri-Film No. 9987).

Compressed Air and Vacuum Lines.—Any convenient method may be used to deliver alternately compressed air and suction to the inside of the glass cylinder. Compressed air and vacuum pressures, as are furnished in the laboratory,

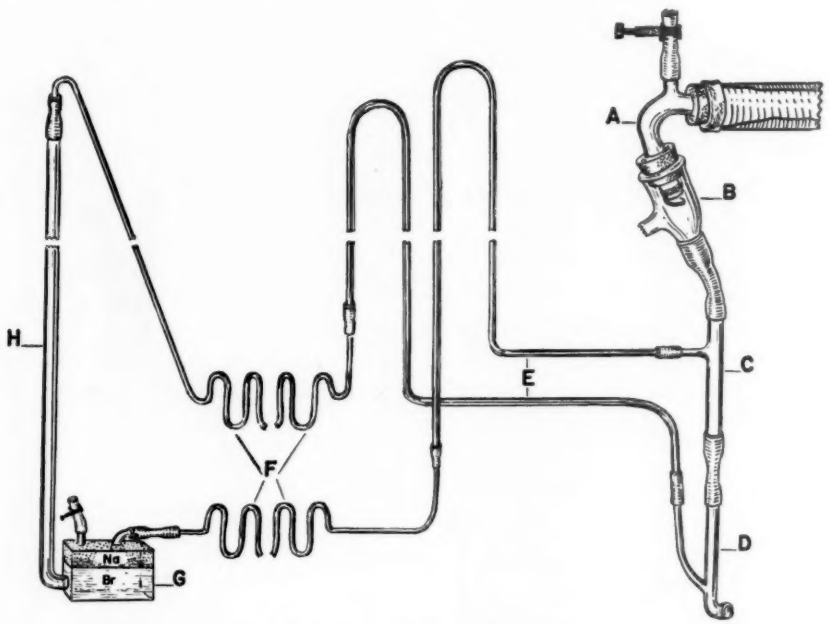


Fig. 7.—The flow meter. *A*, Outflow tube. *B*, ou.flow valve. *C*, glass connecting tube, internal diameter 0.7 cm. *D*, pulmonary artery cannula, internal diameter 0.6 cm. *E*, vertical tubing of flow meter, internal diameter 0.8 cm., height 35 cm. *F*, dampening tubing, internal diameter 0.25 cm., length of each 200 cm. *G*, reservoir; *Na*, saline solution; *Br*, brombenzene solution colored with sudan IV. *H*, manometer, internal diameter 0.4 cm., height 95 cm.

must be regulated to suit the needs of the experiment. This has been accomplished by interposing in the compressed air line a 5 L. reservoir with an escape valve and a mercury manometer attached. The vacuum is controlled by interposing a series of underwater suction bottles. A mercury manometer is incorporated in this system as well. The mechanism for alternately interrupting first one line and then the other consists of two eccentric cams on a single axle, rotated by a small motor. An "Erector Set" motor works quite well. Each cam lifts a weighted arm which, when allowed to fall, compresses and occludes a latex tube which carries either positive or negative air pressure to the pumping chamber. The relative duration of each phase of the cycle can be regulated by increasing or descreasing the area of contact of the cam with the weighted arm.

The Flow Meter.—A flow meter which continuously records but does not interrupt the flow is an asset to any pump designed to perfuse the whole circulation. We have incorporated such a flow meter in the pump described (Fig. 7). The mechanics of this flow meter depend upon the fact that as fluid passes

through a rigid tube there is a fall in pressure between two points along the tube related to the rate of flow. Further, this fall in pressure can be accentuated by a decrease in the diameter of the tube between the point at which the first and second pressures are taken.[32]

A side arm is placed below the outflow valve in the glass connecting tube, and a second side arm placed at the lower end of the pulmonary artery cannula (Fig. 5). The first, or upper, side arm is connected by means of glass tubing, filled with saline solution, to a reservoir of brombenzene at the bottom of a glass manometer. The brombenzene is colored with sudan IV. The second, or lower, side arm is attached by means of a similar glass tubing also filled with saline solution, to the top of the brombenzene column. When there is fluid passing through the pump the pressure in the upper side arm from the pump will be greater than that in the lower side arm. This greater pressure in the upper side arm is transmitted to the reservoir of brombenzene. The height to which the column of brombenzene (specific gravity 1.4) rises is dependent upon the difference in the pressure in the upper side arm and in the lower side arm. The greater the flow the greater the difference in pressure in the two side arms and the higher the column of brombenzene. After calibration the height of the brombenzene column may be read directly in terms of cubic centimeters of flow per minute.

If the pulsations from the pump are not dampened, the column of brombenzene will fluctuate widely with each systolic thrust, making reading of the flow difficult. Therefore, approximately 200 cm. of glass tubing with an internal diameter of 2.5 mm. is interposed between the upper side arm and the bottom of the brombenzene column, and a similar resistance is interposed between the top of the brombenzene column and the lower side arm. The fluctuations of the brombenzene column, under these circumstances, are reduced to a minimum, making possible readings of the flow at all times. Naturally, the greater the dampening the longer will be the time that the column of brombenzene takes to reach its absolute height. With the present arrangement, if the pump is set to deliver 1,400 c.c. per minute, the brombenzene column will have attained 70 per cent of its final height after 30 seconds, 98.5 per cent after 45 seconds, and 100 per cent after 50 seconds. There is less lag in the recording of smaller or more gradual changes. Recently there has been devised a modification of the flow meter described by Moe[33] which will permit an accurate and continuous recording of the flow on a kymograph.[34] With this apparatus there is only a slight lag in the recording of rapid changes of flow through the pump.

Method of Assembly

The inflow and outflow units consisting of the glass tubes, rubber stoppers, and valves are first assembled as previously described. The triple thickness of Penrose tubing is placed in the glass cylinder with the excess, untaped tubing projecting from either end. The excess tubing is then stretched over the outside of the glass cylinder. Certain points in the assembling of the pumping chamber are worth detailing.

The outside of each end of the cylinder is wetted with water. All other parts, except the Penrose tubing which comes in contact with the outside of

the cylinder, remain dry; if wet, the rubber stoppers may slip and become dislodged during operation of the pump.

At the inflow end the excess, untaped triple-thickness Penrose tubing is stretched back over the outside of the cylinder. It is important for the assembling of the pumping chamber, and to permit maximum collapse of the tubing during systole, that about 4 to 5 mm. of untaped Penrose tubing are left inside the cylinder. As previously mentioned, it is to encourage collapse of the inflow end first that the untaped tubing is left at this end.

The inflow unit is inserted into the cylinder inside the Penrose tubing. As the stopper is inserted the Penrose tubing will be pushed ahead inside the cylinder, and therefore when the inflow unit is firmly in place there should be 4 to 5 mm. of untaped Penrose tubing inside the cylinder just in front of the rubber stopper. The Penrose tubing is then stretched over the opposite or outflow end of the glass cylinder. At this end enough tension is placed on the Penrose tubing to make the end of the encircling tape exactly flush with the end of the glass cylinder. The outflow unit is then inserted and, as did the inflow unit, pushes the Penrose tubing ahead of it. At the outflow end, when the rubber stopper is firmly in place, the tape surrounding the Penrose is exactly flush with the end of the rubber stopper. If the units have been properly assembled the enclosed Penrose tubing should be evenly taut but under no tension.

In a few experiments, with survival of the dog as the object, aseptic technique was used. The pump was sterilized in the following manner: The glass cylinder, the Penrose tubing and the inflow and outflow units were assembled prior to sterilization. The side arm attached to the glass cylinder was closed off by a clamp on the attached piece of rubber tubing. The pump was then immersed for eighteen hours in 1:1000 aqueous Zephiran solution after the solution was flushed through the pump to fill it. If the individual parts of the pump are sterilized separately in the Zephiran solution prior to assembly, the glass and rubber become so slippery that assembly is difficult. Inasmuch as the blood never comes in contact with the outside of the Penrose tubing in the glass cylinder it is not necessary that it be sterile. Both the venous and arterial cannulae with their rubber connecting tubes to the inflow and outflow tubes attached, are likewise sterilized in Zephiran. Zephiran is used for these parts because it is not desirable to subject the reinforced Penrose tubing or the polyethylene tubing to heat sterilization.

The only remaining glass tubing that is sterilized is that leading to the manometer of the flow meter, including the vertical tubing (Fig. 7, *E*) from the outflow tube and the arterial cannula leading to the small bore tubing (Fig. 7, *F*) used for dampening the pulse wave. The small bore dampening tubing and the manometer are not sterilized. The vertical tubing, like the rest of the pump, is first filled with sterile saline solution before it is connected to the small bore tubing (Fig. 7, *F*). The saline solution in the dampening tubing and the flow meter manometer is ordinarily not changed from experiment to experiment as there is almost no chance that it will ever come in contact with the blood flowing through the outflow tube.

Operation of the Pump

With the Penrose tubing collapsed, 38 c.c. of fluid is required to fill the pump exclusive of the cannulae. The Penrose tubing when distended maximally inside the glass chamber will hold an additional 32 c.c. This latter figure is therefore the maximum stroke volume. The maximum flow through the pumping chamber has been found to be 4,700 c.c. of water per minute. With cannulae suitable for the vessels of a 15 to 25 kg. dog, a flow of 2,500 c.c. can be obtained. This is well above the vena caval flow of the animals used in these experiments.

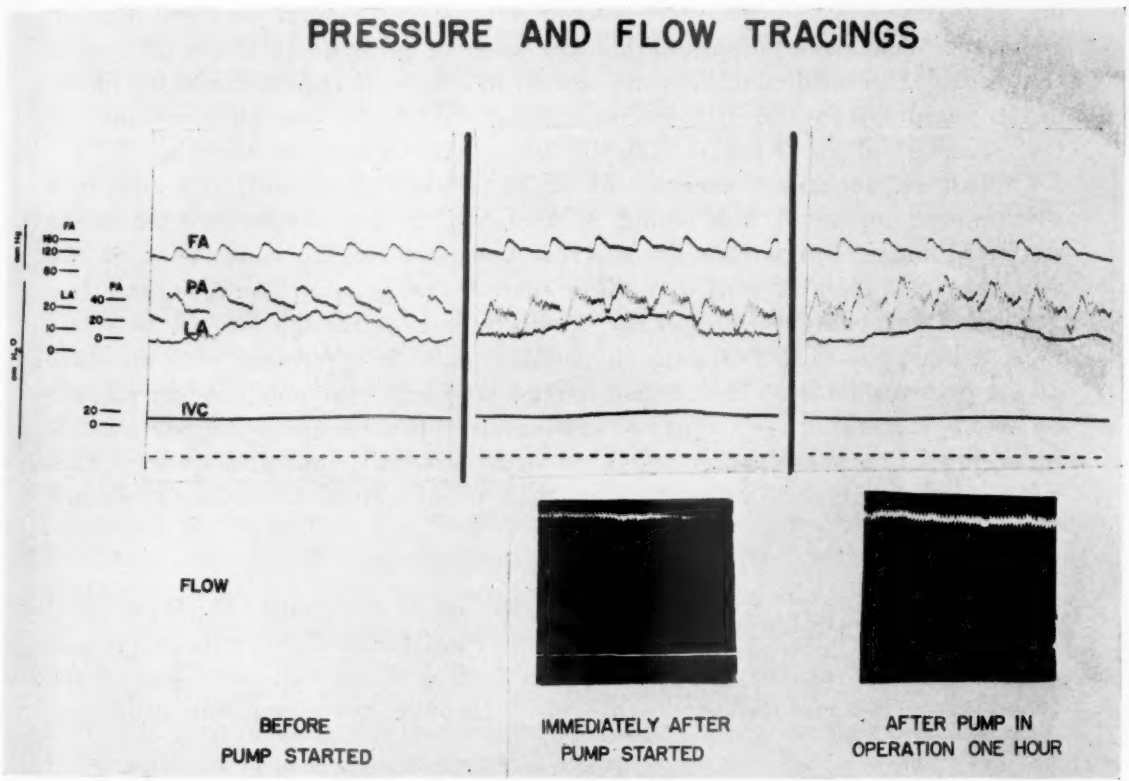


Fig. 8.—Experiment 14. Hamilton manometer recording of blood pressures. *I.V.C.*, inferior vena cava; *L.A.*, left auricle; *P.A.*, pulmonary artery; *F.A.*, Femoral artery.

The flow was recorded by a modified Moe flow meter. After shunting the caval return through the pump for one hour, no significant changes in either pressure or flow were observed in this experiment.

The rate of the pump may be set by regulating the rate at which the cams lift the weighted levers. In vitro studies have shown that a rate of less than approximately 150 cycles per minute does not interfere with the maximum filling and emptying of the pump. We have selected a rate of 108 cycles per minute for routine use as it allows an output well in excess of the venous return through the cavae. The cams may be adjusted so that any ratio of filling to emptying of the pumping chamber can be obtained. We prefer a ratio of 40 for the emptying time, systole, to 60 for the filling time, diastole, as this gives a pulse tracing very similar to that of the normal right ventricle (Fig. 8)

and allows evacuation of the veins by a suction low enough to cause minimal intimal damage.

Once a ratio of systole to diastole has been set it cannot be changed without stopping the pump; but the pressure and vacuum may be adjusted according to the needs of the experiment. The pressure should be set at a small margin (approximately 20 mm. of mercury) above the minimum required for the pump to empty completely on every systole. Too high a pressure causes a very high and abrupt pulse wave and too low a pressure will allow the pump to fill with blood, a state of "congestive failure." We have found the optimal level of pressure to vary somewhat from one experiment to another, depending upon the flow required, but it usually falls between 120 and 160 mm. of mercury. This does not mean that the systolic pressure in the artery rises that high. A great deal of pressure is used to overcome the inertia of the blood in the pumping chamber and outflow tubing, and to overcome the resistance to the movement of the blood through the tubing and the arterial cannula.

With an unlimited reservoir of blood to draw from and with adequate suction, the intake of fluid could be increased to the maximum theoretical stroke volume. But with a limited reservoir, such as the vena cavae of the dog, injury to the vein wall will follow suction that is much stronger than that required to evacuate the vein of the venous return. Although the vein may collapse around the cannula during the suction phase, it is released with the start of the pressure phase. The suction is regulated when the pump is first started by slowly increasing the amount of vacuum until the flow meter registers maximum flow. It is then further increased an additional 10 mm. of mercury. This extra suction will then automatically take care of a sudden increase in venous return.

RESULTS

The following experiments were carried out to determine the efficiency of the pump in performing the function of the right heart; further, to investigate changes in the cellular components and hydrogen ion concentration of the blood after the circulation of the blood through the pump for prolonged periods.

A. *Nonsurvival Experiments—Physiologic Studies.*—I. a. Comparison of blood pressures in the vena cava, the left auricle, the pulmonary artery, and the femoral artery before, during, and after shunting of the venous blood through the pump.

b. Comparison of blood pressures in the pulmonary and femoral arteries before and during shunting of the venous blood through the pump following:

1. A momentary interruption of the venous return

2. A sudden increase in pulmonary vascular resistance as a result of increased intra-alveolar pressure

3. A sudden increase in systemic arterial resistance following the administration of Adrenalin

II. Comparison of arterial and venous oxygen saturation before and after prolonged shunting of the venous return through the pump.

III. Comparison of plasma hemoglobin, hydrogen ion concentration, hematocrit, white blood cell and platelet counts before and after the shunting of the venous blood through the pump.

B. *Survival Experiments.*—The aforementioned experiments completed, three additional experiments were carried out under sterile conditions, with the survival of the dogs as their object.

A. *Nonsurvival Experiments.*—I. a. and b. Change in venous and arterial blood pressure following shunting of the vena caval blood through the pump.

Method: A small caliber polyethylene tube was passed through the femoral vein and into the lower abdominal portion of the inferior vena cava. Pressures were then recorded by attaching this tubing to a sensitive membrane on the Hamilton manometer or by taking direct readings from an attached saline manometer. Pulmonary artery pressure was recorded through a length of polyethylene tubing inserted into the pulmonary artery through the pulmonary artery cannula. Left auricular and systemic arterial pressures were recorded through one of the pulmonary veins and the femoral artery exposed in the groin, respectively.

Many times during the course of a number of experiments the venous return was made to pass through the pump and then back through the right heart. This shunting of the blood through the pump was done by tightening the double loops of silk around the cavae and enclosed venous cannula.

When the positive and negative air pressures delivered to the glass chamber were properly adjusted, there were no significant differences between the arterial and venous pressures taken at the time the venous blood was passing through the heart and at the time it was passing through the pump, described hereafter as the heart period and pump period, respectively. If the venous return were shunted through the pump for more than an hour a gradual fall in all pressures was usually seen (Table I). It is probable that in some experiments this fall in pressure was due to a gradual deterioration of the animal. Blood transfusions were used in many of the experiments. When adequate blood was given, the fall in pressure was usually less marked during the pump period. It is believed that Experiment 14 (Fig. 8), for example, shows no significant difference between the blood pressures taken during the heart period and those taken after the venous blood had circulated through the pump for one hour, principally because of the 400 c.c. of blood that were transfused. No decrease in flow through the pump was evident in this experiment. A fall in flow in other experiments preceded a decline of the systemic arterial pressure.

Following a sudden increase in the venous return the changes in venous and arterial pressure during the heart period and during the pump period were almost identical. The increase in venous return was due to the release of the blood in the cavae occluded for 30 to 60 seconds. Following a moderate increase in intra-alveolar pressure and consequent increase in pulmonary vascular resistance, the rise in systemic venous pressure and fall in systemic arterial pressure were again almost identical in the heart period and in the pump period. However, when the pressure in the alveoli was further increased the pump was more efficient

TABLE

EXPERIMENT	TIME ON PUMP (MINUTES)	HEMATOCRIT (% PACKED R.B.C.)			WHITE BLOOD CELLS (PER CU. MM. IN THOUSANDS)			PLATELETS (PER CU. MM. IN THOUSANDS)		HYDROGEN ION CONCENTRATION (PER CU. MM. IN THOUSANDS)		
		BO	BP	WP	BO	BP	WP	BO	BP	WP	BO	BP	WP
4	36	46		54	14.30		21.85	306	253	7.53	7.14	7.23
5	39	48		46	16.20		16.15	251	198	7.48		7.01
10	57	48	44	23	10.60	3.25	5.20			7.49	7.29	7.16
11	98	47	54	43	15.90	17.00	15.95			7.44	7.35	7.21
12	94				14.50	4.30	5.50			7.50	7.35	7.08
14	101	34	43	42	12.55	5.40	5.80	355	300	7.48	7.30	7.30
16	73	38	35	33	9.40		5.40			7.32	7.00	6.68
17	98	45	45	41*	8.90†		3.90*†			7.27	7.28	6.97*
SS-1	61		45	42							7.13	7.22
SS-2	82		37	41							7.35	7.24

*Air embolus occurred just prior to the taking of final pressures and samples of blood.
†Duplicate counts were not made.
BO, before operation; BP, before pump started; WP, with pump in operation for time noted in Column 2.
SS-1 and SS-2, survival experiments.

in forcing blood through the distended lung than was the right heart. There was also little difference between the pressures taken during the heart period and during the pump period after an increase in vascular resistance following the intravenous administration of Adrenalin.

II. *Oxygen studies:*

Arterial oxygen content and arterial and venous oxygen saturation studies were done after prolonged use of the pump.

Method: Specimens of blood were taken under oil before and after shunting of the venous return through the pump. The arterial samples were obtained through the polyethylene tube which had been inserted into the left auricle. Venous samples were obtained in a similar manner from the inferior vena cava. Throughout the experiments 100 per cent oxygen was administered to the animals through an endotracheal tube. The oxygen content of arterial and venous blood and the oxygen capacity of the arterial blood were determined by the Scholander method.[35]

The results of these studies are recorded in Table I. It was found that the arterial blood was nearly always fully saturated regardless of whether the venous blood was delivered to the lungs by the pump or by the right heart. The venous oxygen saturation usually decreased during the time the blood was passing through the pump. An increase in the arteriovenous difference could be correlated with a fall in flow and systemic arterial and venous pressures. The decrease in venous oxygen saturation probably reflected a slowing of the peripheral systemic flow with pooling of the venous blood in the peripheral venules and capillaries. Aside from the trauma resulting from the insertion of the arterial and venous cannula, there is no reason to believe at the present time that a pump which efficiently performs the mechanical function of the right heart is in itself a cause for shock. It is likely that similar changes in the arteriovenous difference would have followed a similar operative procedure in which the blood passed only through the right heart.

TABLE I

HEMOLYSIS (MG. %)			MEAN FEMORAL ARTERY PRESSURE (MM. HG)			TRANSFUSION (C.C. BLOOD)	BLOOD OXYGEN STUDIES							
							ARTERIAL				VENOUS CONTENT (VOL. %)		ARTERIAL-VENOUS DIFFERENCE (VOL. %)	
							SATURATION (%)		CONTENT (VOL. %)					
BO	BP	WP	BO	BP	WP		BP	WP	BP	WP	BP	WP	BP	WP
			175	145	105	0			24.0	23.3	16.4		7.6	
			140	132	80	0								
			150	90	80	375	100+	100+	20.3	14.6	11.3	4.1	9.0	10.5
			120	56	70	360	100+	100+	24.5	18.1	10.9	4.2	13.6	13.8
30.0	38.0	88.0	135	90	100	220	88	93.7	19.6	17.0	7.3	4.5	12.3	12.5
4.3	63.0	304.0	120	110	110	400	100+	100+	18.7	19.2	11.6	9.8	7.1	9.4
1.2	40.0	110.0	144	92	70	500	100+	100+	20.3	16.5	8.8	3.5	11.5	13.0
2.5	7.8	408.0*	156	124	60*	200	100+	65.8*	24.8	11.8*	12.3	4.4*	12.5	8.3*
	1.0	60.0				375					13.8	10.6		
	15.3	99.0				475					14.0	10.9		

III. *Changes in the cellular components and pH of the blood:*

Method: Hematocrit, plasma hemoglobin, pH determinations, and white blood cells and platelet counts were made on peripheral venous blood once or twice before the pump was started and then again at the end of the run on the pump. Plasma hemoglobin, a measure of hemolysis, was determined by the Bing and Baker[36] benzidine method as modified by Bauer and Wood.[37] Platelet counts were determined by the Nygaard-Adams method.[38]* Hydrogen ion concentration of the plasma was determined anaerobically in the Beckman pH meter.

Results: The results of these studies in several experiments are recorded in Table I. In the experiments recorded the majority of studies were carried out. They include the experiments with the greatest and the smallest changes observed following shunting of blood through the pump. In the second column of this table the length of time, in minutes, that the animal's venous return was passing through the pump is recorded. Usually, the pump was continued in operation for a short time after the studies on the pump were completed. In all of the experiments the blood oxygen and pressure studies were done at the time recorded in the second column, with the pump still in operation. In most of the experiments, the other studies listed in this table as having been done during operation of the pump were done at this time also. Occasionally, however, the last white blood cell counts, hematocrit, and pH determinations were made after the pump had been stopped and the blood was again passing through the right heart.

Hemolysis of red cells occurring during the experiment was seldom marked and did not at any time exceed 2 per cent of the estimated total circulating red cell mass. It is evident from the control determination done before operation and the determination done after operation and heparinization, but before the pump was started, that some of the hemolysis of red cells was due to factors other than the passage of the blood through the pump.

*We are indebted to Dr. James E. Smith for the platelet count determinations.

In the experiments where white blood counts were done before and after the pump period, a change in the number of circulating white blood cells was never marked. There was frequently observed, however, a fall in the number of circulating white cells between the time the operative procedure was begun and the pump was started. Experiments 4 and 5 were exceptions to this. It is of interest that no transfusions were given in either of these two experiments.

Following the prolonged shunting of the venous blood return through the pump, a moderate fall in the number of circulating platelets was found in the three experiments in which this study was made. The fall was similar in each experiment. In all experiments the hydrogen ion concentration revealed a progressive change from alkalinity to acidity. The type of artificial respiration used may have been partly responsible for this change, which began before the pump was started. The positive pressure apparatus used did not permit maximum ventilation. Inadequate ventilation has been shown to be a cause of acidosis.[5] Sodium bicarbonate was given intravenously in some of the experiments in an attempt to lessen the degree of acidosis.

B. *Survival Experiments.*—The foregoing experiments indicate that the venous and arterial pressures, the oxygenation, and the composition of the cellular elements of the blood were not, as a rule, significantly altered following shunting of the venous return through the pump. In the remaining experiments aseptic precautions were taken and, after shunting of the venous return through the pump for an hour or more, the cannulae were removed and the incision in the pulmonary artery was repaired in order to allow the animal to survive.

Surgical technique: The protocol of the first experiment in which survival of the animal was the object is summarized below, with emphasis on the surgical technique. In this animal, as well as others included in this group, no attempt was made to open the heart. The technique used in this experiment is essentially the same as was used in all of the experiments in which survival was planned.

On June 24, 1949, a 10.3 kg. young female mongrel dog was anesthetized with 5 per cent sodium pentobarbital, 35 mg. per kilogram, administered intravenously. The right side of the neck and chest was then clipped and shaved and the skin prepared with soap and water, ether, and kalmerid solution. An endotracheal tube of the Hoffman type, with an inflatable cuff, was then passed and held in position by securing to the animal's jaws.

The pump and accessories, assembled and sterilized as previously outlined, were removed from the Zephiran solution in which they had soaked for the previous eighteen hours, and all parts were carefully flushed and then filled with sterile saline solution. The pump was then placed in the sterile clamp attached to a ring stand on an adjoining movable table, and the connection between the pump and the pressure lines was then made by an unscrubbed attendant. The pump was now ready for attachment to the dog by the arterial and venous cannulae.

With the dog lying on the left side, an incision was made along the course of the right fourth rib and the pleura entered through the fourth interspace.

Prior to the opening of the pleura the endotracheal tube was attached to the artificial respiration apparatus through which 100 per cent oxygen was delivered. Positive endotracheal pressure was maintained throughout the operation.

The right pulmonary artery was dissected free of the surrounding tissue, the dissection being carried well into the mediastinum. Double loops of heavy braided silk were then passed, but not tightened, around the primary branches of the right pulmonary artery for the purpose of preventing backflow of blood when the arterial cannula was in position.

An incision was then made in the neck just above the right first rib, and a 2 inch sement of the lower portion of the right external jugular vein was isolated. A ligature was placed around the upper end of the exposed portion of this vein and tied. A second ligature was placed, but not tied, around the exposed vein just above the first rib. The dog was then heparinized by the intravenous administration of 5 mg. of heparin per kilogram body weight. A Blalock clamp was then placed and closed on the right pulmonary artery, as close to the main pulmonary artery as possible. The two primary branches of the right pulmonary artery were occluded by the double loops of silk thread which had been placed around each of them. The threads were then held taut by the weight of hemostats clamped to their free ends. A transverse incision was made in the main right pulmonary artery approximately 1½ cm. distal to the Blalock clamp. The pulmonary artery cannula, its mouth directed toward the left lung, was inserted into the artery and tied in place with the previously described handbraided silk ligature. The arterial cannula and the side arm to the flow meter (Fig. 7) were filled with saline solution. A transverse incision was then made in the vein just above the second ligature and the anterior wall of the opened vein grasped with a small hemostat. The previously prepared plastic venous cannula, with a short segment of rubber tubing attached to its upper end, was slipped into the external jugular vein and directed towards the heart. The hand of an assistant guided the tip of the cannula through the right auricle into the thoracic portion of the inferior vena cava. Bleeding from the upper end of the cannula was controlled by placing a clamp on the segment of rubber tubing at the upper end. Once the venous cannula was in place the ligature around the external jugular vein and enclosed venous cannula was tied. The pump was suspended directly over the operative field and the arterial and venous cannulae were attached to the outflow and inflow tubes respectively. The connections of the outflow unit to the flow meter were also made, taking care that no bubbles of air were trapped in the flow meter tubing. The Blalock clamp was then removed from the right pulmonary artery. The clamp previously placed on the rubber tubing at the junction of the venous cannula with the inflow tube was now slowly released as the pump was started. Air bubbles, not detected and removed during the initial filling of the pump with saline solution, were thus forced through the pump and were removed from one of the side arms attached to the inflow and outflow tubes. The pump was stopped momentarily by clamping the inflow tube during removal of the air. When air removal was complete the clamp on the inflow tube was again released and suction was again slowly increased until maximum flow was registered by the flow meter. The

degree of collapse of the superior and inferior vena cavae during the suction phase was also noted. The previously placed double loops of heavy silk surrounding the superior and inferior vena cavae were then pulled taut, thus preventing any possible flow of blood into the right auricle. The pump was kept in continuous operation for sixty-three minutes. At the end of this time the silk loops around the superior and inferior vena cavae were released and a clamp was placed across the segment of rubber tubing connecting the venous cannula with the inflow tube. This shift back to the right heart caused no apparent change in the condition of the animal. The tie around the venous cannula and external jugular vein was cut and the cannula removed. The

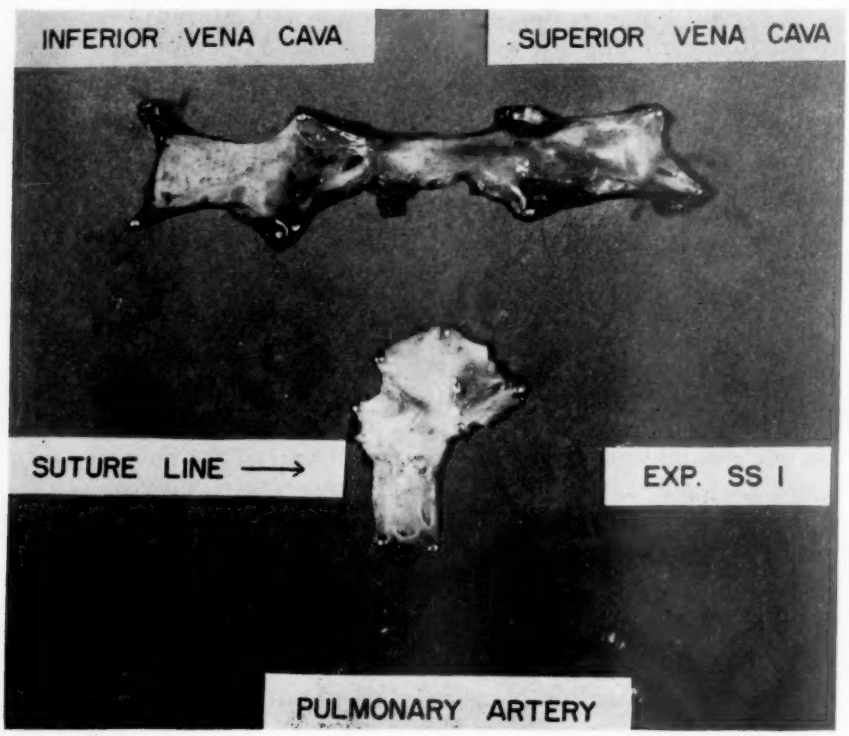


Fig. 9.—Experiment SS-1. Three months prior to sacrifice, venous return shunted through pump directly into right pulmonary artery for sixty-three minutes. There is no gross evidence of damage to the intima of the pulmonary artery or either vena cavae as a result of the ties placed around the arterial or venous cannulae.

vein was then tied below the incision in its wall. The Blalock clamp was then replaced around the right pulmonary artery. Just as this was being done the pulmonary artery cannula, inadvertently being used for traction to expose the mediastinal portion of the pulmonary artery, came out. Bleeding was controlled by finger compression until the Blalock clamp was tightened proximally. The transverse incision in the artery was then sutured with 00000 Deknatel silk and an everting mattress stitch. The suture line completed, 100 mg. of protamine sulfate* were given intravenously. The double loops of silk around the

*The protamine used in these experiments was kindly furnished by Dr. W. R. Kirtley of Eli Lilly & Company, Indianapolis, Ind.

branches of the right pulmonary artery and the Blalock clamp on the proximal pulmonary artery were removed. The right lung was fully inflated and the chest closed. The chest was not drained. During the procedure 375 c.c. of blood and 250 c.c. of normal saline solution, plus 100 c.c. of 3.75 per cent sodium bicarbonate, were given intravenously. Penicillin, 400,000 units, was administered intravenously during the procedure and was continued postoperatively in doses of 300,000 units once or twice daily for a week. The dog showed some weakness of the right foreleg, which may have been constricted by the rope placed around it to hold it out of the operative field. Within about ten days, however, the dog had made a complete recovery. Three months later the dog was sacrificed. At autopsy there was no evidence of ill effects from either the venous or arterial cannulae (Fig. 9).

A similar procedure was carried out on a second dog. In this experiment the venous return was shunted continuously through the pump for 105 minutes. The animal made an uneventful recovery and at sacrifice three months later showed no apparent ill effects from cannulation of the veins or artery. The third animal, during operation of the pump, developed cardiac arrest from the failure of the artificial respiration apparatus to keep the lungs inflated. In none of these experiments was an attempt made to open the right heart. With improvements in technique, intracardiac procedures should be possible, and further experiments are now in progress.

COMMENT

As pointed out in the introduction, others before us have used compressed air as a means of propelling the perfusate. Further, Knowlton and Starling[39] in their heart-lung preparation, showed a glass cylinder with an enclosed thin rubber tube, an apparatus very similar to the pump described in this paper, but used to create a resistance to flow rather than to propel the fluid. Of the pumps using air compression of the perfusate, the pump described by Crafoord is most similar to the one described here, although negative pressure was not employed in his pump to draw blood into the pumping chamber. The maximum minute stroke volume of Crafoord's pump, as reported by Björk[4] is considerably less than that of our pump. We have not attempted to increase the over-all size of the glass cylinder described, but it is theoretically possible, by increasing both the diameter and the length of the glass cylinder, as well as the enclosed compressible rubber tubing, to increase further the maximum stroke volume. An increase in the length without an increase in the diameter of the glass cylinder will not result in an increased minute volume with the present arrangement for delivery of negative and positive pressure to the cylinder.

When the work on the pump was first begun by one of us (W. H. S., Jr.), Mr. James H. Halkett gave valuable advice and assistance in some of the early experiments which were done on cats. We are indebted to him for suggesting the type of valve used in the pump. The valves are similar in action to those described by Gibbs. By making use of the opposing flaps of a toy noisemaker, however, the addition of "chorda tendineae," such as Gibbs used, was not necessary.

An important feature of this pump is the single vena caval cannula. A cannula of the size used in these experiments will not remove the venous blood of the dog as rapidly as it reaches the cavae, unless suction is applied. If gravity were depended upon, a collecting reservoir would have to be placed more than thirty-six inches below the level of the animal's heart in order to keep the vena cavae empty of blood. The suction needed to remove the venous return through a single cannula is, of course, much greater when the pump is suspended above the chest. It would be ideal for a number of reasons to have the pump on an adjacent portable table at the level of the animal's heart. There is no question in our minds, however, that the use of a single venous cannula is superior to the use of two separate venous cannulae for each cava. Polyethylene tubing possesses all the qualities desirable for a single venous cannula. Another method we have used for removing the caval blood is to place a single cannula directly into the right auricle through the auricular appendage. Such a method would have the added advantage of simultaneously removing the coronary vein return. With an auricular cannula, a bubble trap placed between the auricle and the pump is necessary if the heart is opened.

Upon sacrifice of the survival animals there was observed no evidence of intimal damage as a result of the ligature placed around the pulmonary artery cannula. We believe that the failure to find any gross change in the intima may be attributed to several factors: The first, and possibly the most important, factor is the ability of the intima to recover from the effects of moderate trauma. Previous experience[40] with the cannulation of the inferior vena cava and portal vein of more than twenty dogs with small plastic tubing for four to sixty days, revealed only a single instance of occlusion of the vessel due to thrombosis. This was surprising in view of the fact that definite local thrombosis and fibrous tissue formation were found in the veins examined with the tubes in place. Further,[41] where the tube was accidentally or deliberately removed and the vein examined some time later, there was either little or no evidence of the previous trauma to the intima. Second was the use of the hand-braided silk ligatures as suggested by Hufnagle.[42] The multiple point fixation of the artery to the cannula with this tie caused minimal intimal damage. Third was the use of an arterial cannula with a rounded lip and a well-formed groove behind it, allowing the ligature a good hold on the artery wall and minimizing the danger of the lips cutting into the intima of the artery. Fourth is the fact that the intima of the pulmonary artery is relatively thinner and less brittle than that of a systemic artery and fracture of the intima is, therefore, less likely.

We believe that this pump will have its greatest usefulness in the experimental laboratory. Many basic problems in physiology and surgery remain to be solved before operations on the open human heart should be attempted. We are continuing experiments to test the feasibility of shunting the pulmonary venous return from one lung through the pump into a systemic artery. Then, by the use of two pumps, one to by-pass the right side of the heart and the other to by-pass the left side of the heart, the heart can be completely isolated, except for the coronary flow, from the vascular system. It is probable, however, that in order to correct surgically many congenital and acquired lesions

of the interior of the heart, it will be necessary to by-pass only one side of the heart. This is only one of the many important issues that must be settled in the experimental laboratory. In time, the use of this pump as described in these experiments may prove practical for use in the human being. It would seem, however, that the extracorporal oxygenation of the blood, if it is improved (and there is every indication that it will be), would be more satisfactory. The simple construction and large minute stroke volume of this pump suggest that it may be adapted for use with an extracorporal oxygenator as was the pump described by Crafoord.

SUMMARY

A simple perfusion pump with a maximum minute stroke volume of 4,700 c.c. of water has been described. This pump has been used successfully in the dog in place of the right side of the heart, the entire vena caval blood flow being shunted directly into the pulmonary artery. Changes in the cellular components of the blood and in the arterial and venous pressures were studied before, during, and after the venous return was passing through the pump. In several animals the entire vena caval return was made to pass through the pump for prolonged periods, with survival of the animal as the object. The technique employed is described in detail.

Acknowledgment.—The authors wish to express their deep appreciation to Dr. Gustaf E. Lindskog for his encouragement in beginning this work and for his continuing interest and advice. They would also like to thank Misses Jean McCray, Regina H. Kruk, Alice J. Bush, Lilee R. Betty, and Frances R. Ginsberg for their technical assistance in the experiments. They are grateful also to Misses Elizabeth Tuthill and Frances M. Korb for their assistance in the chemical analyses performed. Further, they would like to express their appreciation to Mr. Franklin Hutchinson for his helpful advice in the construction of the flow meter.

REFERENCES

1. Gibbon, J. H., Jr.: Artificial Maintenance of Circulation During Experimental Occlusion of the Pulmonary Artery, Arch. Surg. **34**: 1105-1131, 1937.
2. Gibbon, J. H., Jr.: Maintenance of Life During Experimental Occlusion of the Pulmonary Artery Followed by Survival, Surg., Gynec. & Obst. **69**: 602-614, 1939.
3. Gibbon, J. H., Jr., and Krawl, C. W.: An Efficient Oxygenator for Blood, J. Lab. & Clin. Med. **26**: 1803-1809, 1941.
4. Björk, V. O.: Brain Perfusions in Dogs With Artificially Oxygenated Blood, Acta chir. Scandinav. (suppl. 137) **96**: 1-122, 1948.
5. Crafoord, C.: Some Aspects of the Development of Intrathoracic Surgery, Surg., Gynec. & Obst. **89**: 629-637, 1949.
6. Jongbloed, J.: Het Mechanische Hart, Nederl. tijdschr. v. geneesk. **92**: 1065-1072, 1948.
7. Jongbloed, J.: Mechanisch Hart-Longsysteem, Nederl. tijdschr. v. geneesk. **93**: 548-552, 1949.
8. Jongbloed, J.: The Mechanical Heart-Lung System, Surg., Gynec. & Obst. **89**: 684-691, 1949.
9. Karlson, E., Dennis, C., and Westover, D. E.: Blood Oxygenation. I. The Kolff Apparatus. II. Multiple Horizontal Rotating Cylinders, Proc. Soc. Exper. Biol. & Med. **70**: 223-224, 1949.
10. Karlson, E., Dennis C., and Westover, D. E.: Blood Oxygenation. III. The Vertical Revolving Cylinder. IV. The Vertical Revolving Cone, Proc. Soc. Exper. Biol. & Med. **70**: 225-226, 1949.
11. Karlson, K. E., Dennis, C., Sanderson, D., and Culmer, C. U.: An Oxygenator With Increased Capacity: Multiple Vertical Revolving Cylinders, Proc. Soc. Exper. Biol. & Med. **71**: 204-206, 1949.
12. Jacobj, C.: Ein Beitrag zur Technik der Kuntslichen Durchblutung über lebender Organe, Arch. f. exper. Path. u. Pharmakol. **36**: 330-348, 1895.
13. Embly, E. H., and Martin, C. J.: The Action of Anesthetic Quantities of Chloroform Upon the Blood Vessels of the Bowel and Kidney, With an Account of an Artificial Circulation Apparatus, J. Physiol. **32**: 147-158, 1905.
14. Brodie, T. C.: The Perfusion of Surviving Organs, J. Physiol. **29**: 266-275, 1903.

15. Hooker, D. R.: A Study of Isolated Kidney: The Influence of Pulse Pressure Upon Renal Function, Am. J. Physiol. **27**: 24-44, 1910.
16. Richards, A. N., and Drinker, C. K.: An Apparatus for the Perfusion of Isolated Organs, J. Pharmacol. & Exper. Therap. **7**: 467-483, 1915.
17. Dixon, W. E.: A Simple Perfusion Pump, J. Physiol. **56**: Proc. p. XL-XLII, 1922.
18. De Bakey, M.: A Simple Continuous-Flow Blood Transfusion Instrument, New Orleans M. & S. J. **87**: 386-389, 1934.
19. Van Allen, C. M.: A Pump for Clinical and Laboratory Purposes Which Employs the Milking Principle, J. A. M. A. **98**: 1805-1806, 1932.
20. Dale, H. H., and Schuster, E. H. J.: A Double Perfusion Pump, J. Physiol. **64**: 356-364, 1928.
21. Gibbs, O. S.: An Artificial Heart, J. Pharmacol. & Exper. Therap. **38**: 197-215, 1930.
22. Gibbs, O. S.: An Artificial Heart for Dogs, J. Pharmacol. & Exper. Therap. **49**: 181-186, 1933.
23. Tainter, M. L.: Use of the Gibbs Artificial Heart in the Study of Circulatory Phenomena, With Descriptions of Improvements in the Device, and of Response to Some Drugs, Arch. internat. de pharmacodyn. et de thérapie **42**: 186-199, 1932.
24. Jacobj, C.: Apparat. zur Durchblutung Isolirter überlebender Organe. Arch. f. exper. Path. u. Pharmakol. **26**: 388-400, 1890.
25. Lindbergh, C. A.: An Apparatus for the Culture of Whole Organs, J. Exper. Med. **62**: 409-432, 1935.
26. Barcroft, H.: Observations on the Pumping Action of the Heart, J. Physiol. **78**: 186-195, 1933.
27. De Burgh Daly, I.: Negative Pressure Pulmonary Ventilation in the Heart-Lung Preparation, J. Physiol. **63**: 81-93, 1927.
28. De Burgh Daly, I., and Thorpe, W. U.: An Isolated Mammalian Heart Preparation Capable of Performing Work for Prolonged Periods, J. Physiol. **79**: 199-217, 1933.
29. De Burgh Daly, I., and others: Evaluation of Bronchomotor and Pulmonary Vasomotor Activity by Means of the Perfused Living Animal Under Negative Pressure Ventilation, Quart. J. Exper. Physiol. **31**: 227-262, 1942.
30. Barcroft, H.: A Mechanical Stromuhr, J. Physiol. **67**: 402-408, 1929.
31. Hemingway, A.: Some Observations on the Perfusion of the Isolated Kidney by a Pump, J. Physiol. **71**: 201-213, 1931.
32. Best, C. H., and Taylor, N. M.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins Company, p. 191, Fig. 38.
33. Moe, G. K.: A Simple Technique for Continuous Registration of Blood Flow, Science **109**: 381, 1949.
34. Sewell, W. H., Jr.: Data to be published.
35. Roughton, F. J. W., and Scholander, P. F.: Micro Gasometric Estimation of Blood Gases; I. Oxygen, J. Biol. Chem. **148**: 541-550, 1943.
36. Bing, F. C., and Baker, R. W.: The Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, J. Biol. Chem. **92**: 589-600, 1931.
37. Bauer, J. L., and Wood, T.: Personal communication.
38. Adams, E.: Postoperative Thrombocytosis, Arch. Int. Med. **73**: 329-335, 1944.
39. Knowlton, F. P., and Starling, E. H.: The Influence of Variations in Temperature and Blood Pressure on the Performance of the Isolated Mammalian Heart, J. Physiol. **44**: 206-219, 1912.
40. Cresson, S. L., and Glenn, W. W. L.: Venous Catheterization With Polyethylene Tubing, J. Lab. & Clin. Med. **33**: 1597-1602, 1948.
41. Cresson, S. L., and Glenn, W. W. L.: Unpublished data.
42. Hufnagle, C. A.: Permanent Intubation of the Thoracic Aorta, Arch. Surg. **54**: 382-389, 1947.

FIBROSARCOMA OF THE SOFT TISSUES OF THE EXTREMITIES

A Review of Seventy-Eight Cases

John C. Ivins, M.D.,* Malcolm B. Dockerty, M.D.,† and
Ralph K. Ghormley, M.D.,‡ Rochester, Minn.

FIBROSARCOMA is a malignant tumor which arises from connective tissue. Despite the fact that it is rare, we have found that it is the commonest primary malignant tumor affecting the extremities. Yet, at the time of this report, too little is known about this particular tumor to permit the clinician to decide absolutely the treatment which should be used in any given case and the outcome to be expected. This statement is based on clinical experience and a review of literature on this subject.[1-19]

We are reporting an analysis of our observations of 78 cases of fibrosarcomas of soft tissue, special emphasis having been laid on the correlation between the histologic appearance of the tissue of the tumor and the end results obtained from treatment. An attempt also was made to study the tissues as completely as possible and to group them into 4 grades of relative malignancy on the basis of all the features which they presented.

ANALYSIS OF CASES

As a basis for this study, a review was made of all available records of cases in which the diagnosis was fibrosarcoma of the soft tissues of the extremities, and for which treatment had been carried out at the Mayo Clinic during the 10-year period from Jan. 1, 1931, to Dec. 31, 1940. In 10 cases the diagnosis of fibrosarcoma was found to be erroneous. In order to be certain that a case was not included that might more properly be classed as fibrosarcoma of bone, that is, a fibrosarcoma whose primary origin was from an osseous component, and which secondarily involved the neighboring soft tissues, all cases were excluded in which associated destruction of bone had occurred, regardless of the cause. Our series then included 78 cases. All specimens of tumors were preserved in 10 per cent formalin and were made available for study.

In cases in which amputation had been performed, the distance between the upper end of the tumor and the site of the amputation was carefully measured. On the other hand, if local removal had been accomplished, the amount of tissue sacrificed and its relationship to the size of the tumor were noted. Gross estimates of degrees of encapsulation were made. Multiple blocks were taken from each tumor; selection was designed to sample portions of tumors which were of different color and consistency and also to verify the presence or absence of a capsule. Paraffin sections were made in the usual manner and hematoxylin and eosin stains were employed. Several blocks were treated by other methods to demonstrate the presence of mucus and reticulin.

Abridgment of thesis submitted by Dr. Ivins to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Orthopedic Surgery.

Received for publication, Sept. 26, 1949.

*Section on Orthopedic Surgery, Mayo Clinic.

†Division of Surgical Pathology, Mayo Clinic.

‡Section on Orthopedic Surgery, Mayo Clinic.

In 69 per cent of our cases the patients were males. The ages of the patients ranged from 12 to 76 years, and two-thirds of the patients were in the third, fourth, and fifth decades of life. The average age was 44.7 years.

The patient had given a definite history of some other member of the family having had cancer in 18 per cent of the cases, but a specific history of sarcoma was obtained in only 3 cases. Heredity, however, is not considered a predisposing factor in the development of fibrosarcoma.

In our series of 78 cases, 28 per cent of the fibrosarcomas occurred in the upper extremities and 72 per cent in the lower extremities. The more frequent appearance of the tumor in the lower extremities than in the upper has been ascribed simply to the larger volume of the thigh and leg, as compared with the arm and forearm. The knee, elbow, and forearm were the commonest sites. As a rule, the tumors originate in the subcutaneous tissues and fasciae or from the fibrous intermuscular or intramuscular septa.

The cause of fibrosarcoma is unknown. Trauma has been considered by some to be of etiological significance. In 1907, Segond[18] established certain criteria, since in common usage, that must be fulfilled before the possibility of trauma as a cause is entertained.

In 19 of our 78 cases (about 25 per cent) the patient gave a history of trauma which he considered to be related in some manner or degree to his illness. Of the 19 possible cases in our series in which trauma might have been of etiological significance, however, in only 1 case was it remotely probable that it could have been responsible for inducing malignant change in a benign neoplasm of long standing. In this case, a man 48 years of age had had a mass on the distal portion of the right leg for 30 years. Seven years prior to admission he had been kicked by a calf, after which the mass began to grow. He had had 2 excisions elsewhere for fibrosarcoma, grade 3. The leg was amputated later, and 2 years after the first excision the patient died of pulmonary metastasis.

Fibrosarcomas, unfortunately, do not give rise to alarming symptoms, a fact which may be of significance when the rather grave prognosis associated with them is considered. In all cases in our series the presence of a mass or "swelling" was the initial complaint. In 94 per cent of the cases it was noted that the mass was enlarging. As a rule, enlargement of the mass was slow, but in 14 per cent of the cases it was noted that, after a variable period of apparently static existence or slow enlargement, the tumor mass suddenly began to grow with rapidity. In 4 cases the growth was rapid from the outset. Only 27 of the tumors were primary; the remaining tumors (65 per cent) were recurrences, and the patients had had one or more excisions elsewhere before being seen at the clinic for the first time.

Pain was not a prominent symptom. In only 29 cases of the entire series was pain listed as a symptom, and in only 1 case was the pain severe. In the majority of cases, pain was inconstant; it was usually described as an "aching," at times a "local awareness" or tenderness.

Constant constitutional symptoms were not present. Only 2 patients had lost a significant amount of weight. Laboratory examination of the blood and urine did not disclose any abnormality.

The duration of symptoms, represented by the time between first appearance of symptoms and first visit to the clinic, was known in 75 of the 78 cases. It ranged from as short as 1 week to as long as 30 years, the average duration for the entire series being about 3 years and 2 months.

Roentgenograms showed evidence of a soft tissue mass in 55 per cent of our cases. Although the tumor mass casts a shadow of the same density as the surrounding normal tissue and the presence or absence of infiltrative growth cannot be determined, the relative size of the mass, its proximity to bone or other vital structures, and the presence or absence of local destructive changes in bone are apparent and are of assistance in determining the procedure to be employed.

Edema is present in varying amounts, evidently depending on the extent of local circulatory blockage by the tumor.

The tumor is usually single, but may be multicentric in origin, particularly in the case of recurrent tumors. On palpation, the tumor is not as hard as a carcinoma, nor as soft as a lipoma. Characteristically, there is a firmness rather midway between these extremes; however, cellular fibrosarcomas may give a soft, fluctuant sensation on occasion, while low-grade fibrous tumors may be nearly as hard as bone. The mass is rounded, or lobulated, and as a rule is rather sharply delimited from the surrounding normal tissue. The earlier lesions, and those which are superficially placed, are freely movable, large tumors; those lesions arising from, or attached to, deep fascial structures may be fixed.

There is nothing characteristic about the size of the tumors. In our series the tumors varied in size from small nodules a few millimeters in diameter, to enormous masses weighing several thousand grams. A relationship could not be established regarding the size of the tumor mass, pathologic grade, or end result.

Extension into the lumens of blood vessels is common, hence the majority of these neoplasms metastasize rather early in their development.

MICROSCOPIC FEATURES

The microscopic structure of a fibrosarcoma varies considerably, just as do the gross appearance and clinical behavior. These neoplasms are composed of cells the ultimate function of which is production of fibrous connective tissue. They range from fibrous fibrosarcoma, closely akin to benign fibroma, to cellular fibrosarcoma which exhibits marked anaplasia and pleomorphism. Yet all of them have certain common features which distinguish fibrosarcomas as a definite group of tumors.

The typical cell is the fibroblast, a cell form which is intermediate between the primitive undifferentiated mesoblast from which it arises, and its adult counterpart, the fibrocyte. These cells vary in their degree of differentiation from one tumor to another, but in any one given tumor rather reliable uniformity usually exists. Typically the cells are fusiform or elongated and have been described by the familiar term "spindle cell." There may be some variation in size of the cells and in the amount of intercellular matrix that separates in-

dividual cells. The nuclei are oval to spindle shaped, but may be lobulated. The nuclear chromatin is arranged in reticular fashion and varies considerably in amount from tumor to tumor. Usually a single, distinct, basophilic nucleolus is present, but there may be several nucleoli.

In highly differentiated tumors the acidophilic cytoplasm is rather scanty and is drawn out into long processes at the ends of the cells. Primitive forms exhibit considerable variation in shape and size of the cell, and the amount of cytoplasm is increased. In these forms there may be a definite increase in the amount of nuclear chromatin and large basophilic granules.

The chief function of these cells is fibrogenesis, and they are separated by varying amounts of collagenous argyrophil fibrils arranged in strands. The collagenous matrix is generally homogeneous, but at times it may appear to be myxomatous.

Scattered throughout the tumor are small vessels, few in number in adult types, but characteristically rather abundant in less well-differentiated tumors; many of them are extremely fragile and composed of but a single layer of endothelium. Radiating from these vessels is a delicate network of fibrils which furnishes the supporting stroma and gives rise to the lobulated appearance. In rapidly growing tumors, areas of necrosis are seen at the periphery of the lobules where tumor tissue has grown away from its source of nourishment. Occasionally this may give rise to a peritheliomatous structure. Lymph vessels have not been observed within the substance of the tumors.

Usually the periphery of the tumor is marked by a capsule of sorts. The cells are arranged in several layers in concentric fashion and are flattened, but in other respects they do not seem to differ from the cells to be found elsewhere within the tumor. It can be seen that fasciculations that course between the individual lobules descend from, or are continuous with, the capsule. Here and there the continuity of the capsule is interrupted by actively growing projections of tumor cells that are continuous with both the intralobular tissue and the cells of the capsule. As indicated before, the flattened cells on the periphery probably do not form a true delimiting capsule, but rather they represent a "compression zone" in evidence of the rapid expansive growth of the tumor.

Within the lobules of the mass the fibroblasts arrange themselves in parallel fashion, the degree of this polarity testifying in some measure to the degree of differentiation of the tumor. At times these polarized cells are seen to be grouped in fascicles that may appear to intertwine, or they may form whorls. The exact significance of the presence of pathologic mitotic figures is obscure, although the concensus throughout the literature seems to be that to diagnose fibrosarcoma without having found mitotic figures is a hazardous procedure. Many pathologists hold that they are an evidence of malignancy and represent another manifestation of wild and disordered growth.

As a rule, microscopic study of fibrosarcomas results in diagnosis because of the characteristic structure of these tumors. However, several neoplasms, both benign and malignant, make interpretation of histologic findings difficult at times.

GRADING OF FIBROSARCOMA

Broders first devised a system of pathologic grading which employed the fundamental principle of cell differentiation, wherein 4 grades of malignancy were established, grade 1 being the least malignant and grade 4 the most malignant. This system, as originally devised, was meant to be used as a guide to treatment. Accumulated experience, however, has shown that the grading of tumors, particularly carcinomas, also has definite prognostic significance. Without regard to the treatment employed it is safe to say that, in general, the prognosis is more favorable if the tumor is of grade 1 or 2 than it is if the tumor is of a higher grade. The pathologic grading of sarcomas is more difficult than the grading of carcinomas, principally because the latter more commonly display characteristics of organoid growth, which are relatively easy to recognize as evidence of cellular differentiation. In the case of fibrosarcomas, fibrogenesis is the principal indication of the functioning capacity of the cells. In 1936, Meyerding, Broders, and Hargraves, analyzing an earlier clinic series of fibrosarcomas, found that the grade of the tumor influences the prognoses.[15]

Grade 1.—Of the 78 tumors in our series, 17 (or 22 per cent) were classified as grade 1. In general, they were fibrocellular tumors. As a group, the tumors exhibited abundant fibrogenesis, and the polarity of cells and fibers was additional evidence of relatively adult tissue (Fig. 1 *a*).

Some were composed entirely of the spindle-cell type of tissue and others contained myxomatous tissue. The size or shape of the cells varied little; they were fusiform, not closely packed, and presented spindle-shaped nuclei which did not stain deeply. Dense nucleoli were not a prominent feature. In areas of myxomatous tissue, nuclei lose their fusiform appearance and assume a stellate shape, and the cells usually have little cytoplasm that can be seen (Fig. 1 *b*). Mitotic figures, both normal and pathologic, were present in all tumors, but in some they could be found in almost every field, while in others they were located only after diligent search. The tumors of this grade were not vascular, although some had varying amounts of newly formed, thin-walled vessels. In 2 tumors perivascular disposition of the cells was evident.

In 13 cases the tumors were known to recur. It is probably precarious to assume anything from this fact alone, since in 65 per cent of the cases the patient had had surgical treatment elsewhere, and the extent or adequacy of that treatment was unknown. Nevertheless, of the 17 patients, all except 5 required multiple excisions. Three of the 5 patients who had but 1 excision are well and free from their disease 6, 7, and 15 years later. One died of widespread metastasis 14 months after wide excision of the primary tumor. No report could be obtained concerning the fifth patient.

Of the 12 patients who had multiple excisions, the number of excisions varied from 2 to 10, and 3 patients underwent amputation subsequently.

No correlation can be found between the manner in which patients were treated and the known result. Two of 3 patients who underwent amputation died of pulmonary metastasis, while 1 patient is alive and well after 10 excisions in a period of 13 years. Furthermore, repeated re-examination of the

tissue of the tumors disclosed nothing to distinguish the recurrent tumors from those which existed only as primary tumors. An increase in relative malignancy was not noted in any of the tissue from recurrent tumors which were available for study.

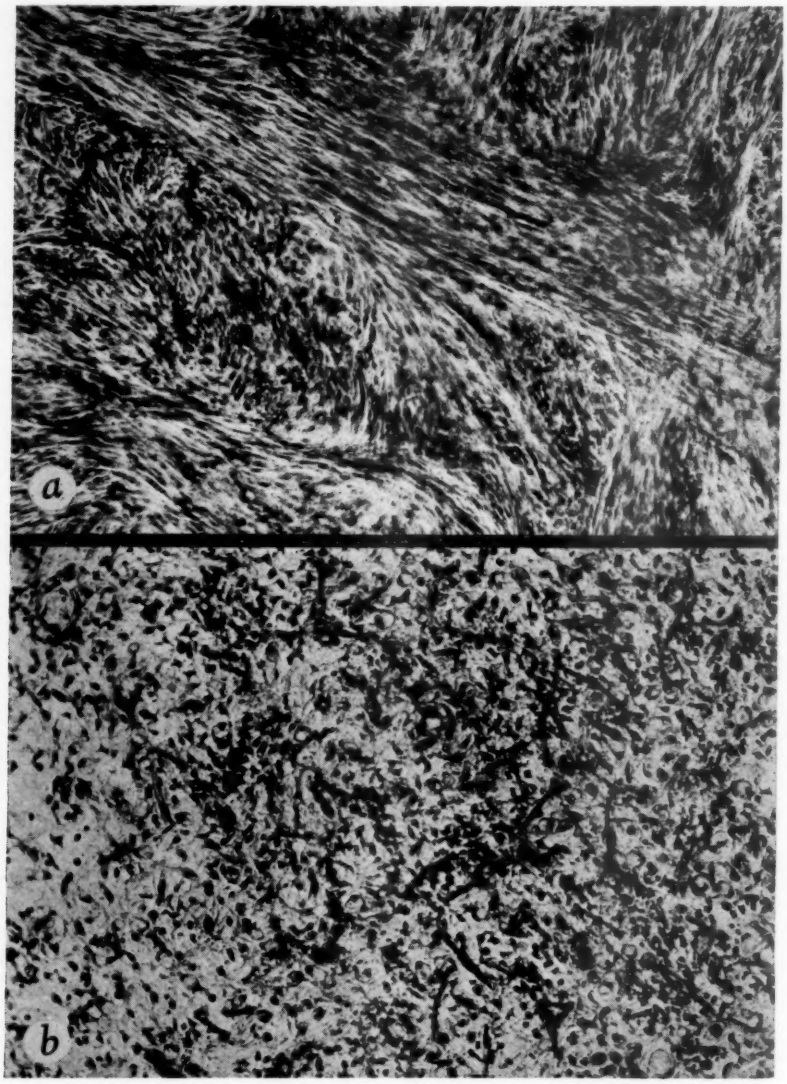


Fig. 1.—Fibrosarcoma, grade 1. *a*, Marked fasciculation in a tumor from the leg of a woman 59 years old who was well for 15 years after 2 excisions and amputation (hematoxylin and eosin, ×100). *b*, Myxomatous structure in the tumor from the upper part of the thigh of a man 50 years old. Final result in this case unknown; 2 excisions were carried out (hematoxylin and eosin, ×100).

The condition of 3 patients could not be followed adequately; however, it is known that 2 of these patients had recurrences. Of the remaining 14 patients, one-half are known to be living and well from 6 to 15 years after treatment at the Mayo Clinic, while one-half are known to have died. It should be noted that the course of the disease was long in all cases in which the patient died; for

example, 1 patient died of pulmonary metastasis 6 years after amputation and 17 years after the onset of illness. These cases illustrate that any determination of the number of 5-year cures has a limited value.

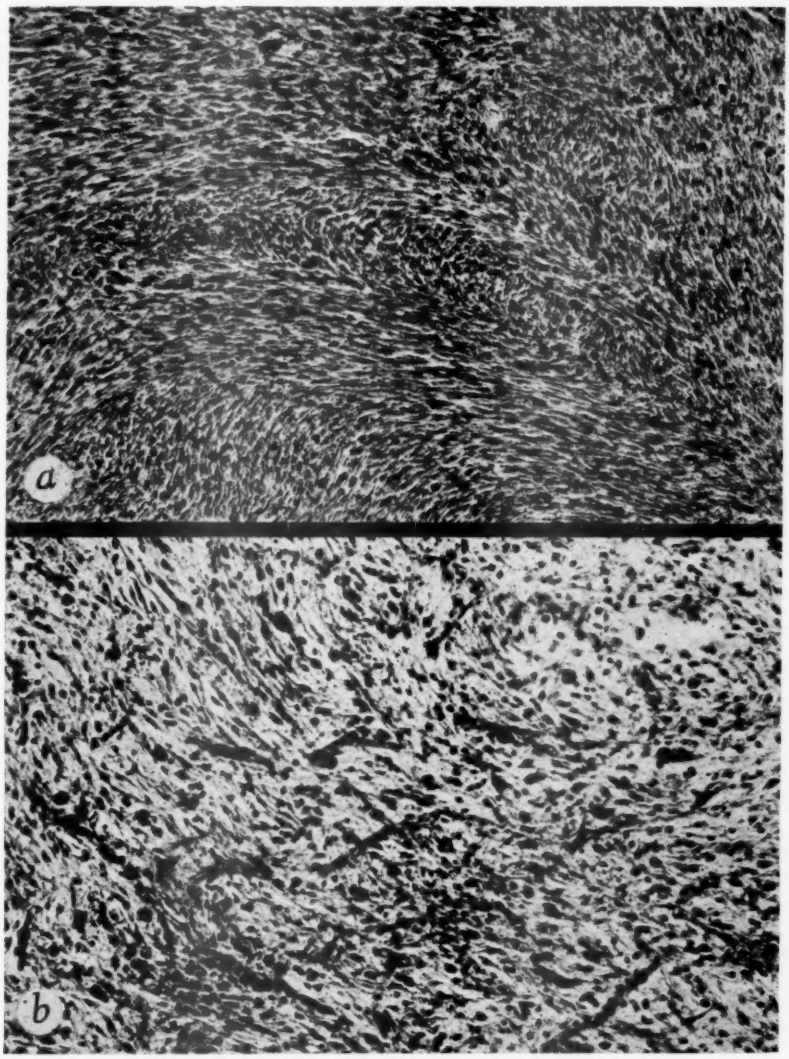


Fig. 2.—Fibrosarcoma, grade 2. *a*, Good uniformity of individual cellular elements and some fasciculation in the lesion from the calf of a man 61 years old. Death, due to pulmonary metastasis after 3 local excisions, occurred 4 years after the last excision (hematoxylin and eosin, ×100). *b*, The myxomatous structure of a lesion from the left thigh of a man 67 years old. Result of treatment is unknown (hematoxylin and eosin, ×100).

Grade 2.—Nineteen, or 24 per cent, of the 78 tumors were of grade 2. With but 1 exception, all 19 tumors were fibrocellular. As a group, the tissues of the tumors exhibited rather abundant production of fibers, but noticeably less than was evident in the tumors of grade 1. One tumor was predominantly cellular; the course of the disease in this case was not particularly short.

In regard to giant cells, fibrosarcomas, grade 2, could not be distinguished from fibrosarcomas, grade 1. In none of the sections were foreign-body giant

cells seen; in only 2 tumors were tumor giant cells evident, and these in limited number. Nothing about the course of the disease in these 2 instances set them apart. One patient died of pulmonary metastasis and at the time of this report the other remains alive and well 13 years after surgical excision of the tumor.

Individual cellular elements were not markedly different from those of tumors classified as grade 1 (Fig. 2 *a*); in general, rather uniform spindle cells predominated. Only 3 tumors of grade 2 contained myxomatous areas (Fig. 2 *b*). The nucleoli were more prominent in fibrosarcomas of grade 2 than in those of grade 1, and, as a group, the tumors also were more vascular than the tumors of grade 1. A possible relationship between these two observations is conjectural.

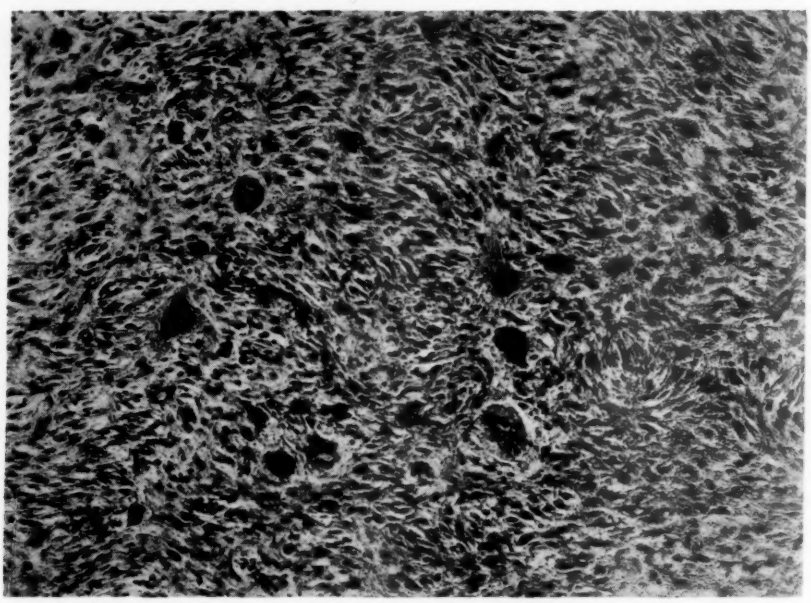


Fig. 3.—Fibrosarcoma, grade 3, illustrating giant cells and disorderly growth pattern. Lesion was from a man 49 years old who had a recurring mass on volar aspect of left forearm. Death occurred from pulmonary metastasis 16 months after amputation. Total course was 4 years (hematoxylin and eosin, ×100).

Mitotic figures were present in increased numbers, a manifestation of increased cellular activity. Peritheliomatous structure was evident in 1 tumor in this group.

Here again recurrence was the rule. In 13 of 15 cases in which definite information was available, there were from 1 to 4 recurrences. The condition of 4 of the 19 patients could not be adequately followed. Of the remaining 15 patients, 8 are known to have died of their disease. This result is the same as that obtained for tumors of grade 1.

Grade 3.—Of the 78 tumors, 29 (about 37 per cent) were classified as grade 3. The tumors, with but 4 exceptions, were all fibrocellular. A striking feature was the increased number of tumor giant cells; in 17 tumors the number was significant (Fig. 3).

The individual cellular elements tended to be smaller, more closely packed, and darker staining than those of other tumors. Variation in size and shape of cells was greater in tumors of this grade than in tumors of lower grades; in some of them spindle-shaped cells were present, but generally the cells tended to be more plump or rounded in appearance. In most of the nuclei 1 small, dark, prominent nucleolus was prominent, but at times 2 or more nucleoli were apparent. Rather striking was the increased number of mitotic figures to be found. In almost all tumors at least 1 mitotic figure could be found in each oil immersion field. The vast majority of these mitotic figures appeared entirely normal, yet all manner of so-called abnormal mitotic figures could be found with some search. Scattered areas of hemorrhage and hyaline necrosis were much more frequently seen in these tumors than in those of lower grades, and, as a group, they were rather well supplied with thin-walled, newly formed vessels.

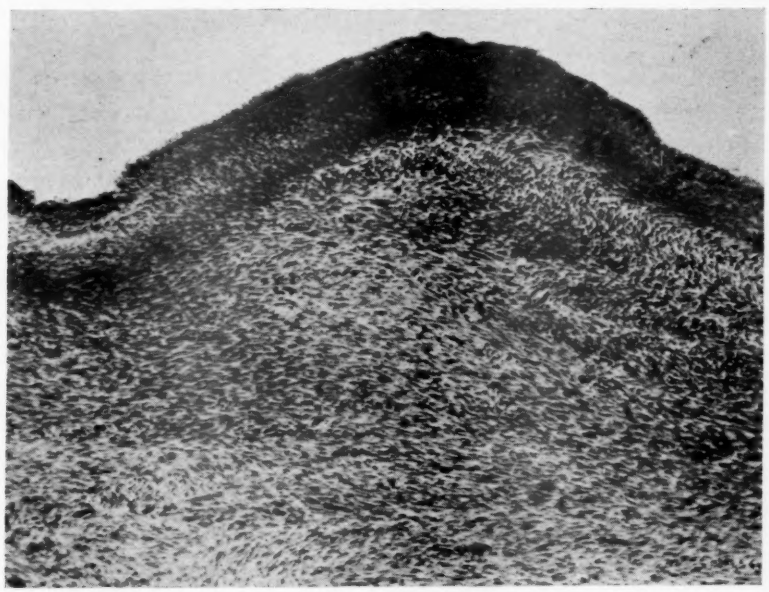


Fig. 4.—Fibrosarcoma, grade 3, illustrating the pseudocapsule or compression zone composed of actively growing tumor tissue. Lesion is from a man 25 years old who had a recurring mass on the lateral aspect of left elbow that followed local contusion. Three excisions were done. The patient was alive and well 15 years after the last excision (hematoxylin and eosin, ×50).

Less than one-third of these tumors contained myxomatous areas. In the tumors of lower grades the myxomatous areas tended to be diffuse; in fibrosarcomas of grade 3, myxomatous patches were intermingled with portions of denser tissue. In dense areas, polarity was not a prominent feature because of both the reduced fibrogenesis and the change in general shape of the cells (Fig. 4).

Recurrences were evident in 19 of the 29 cases, the number varying from 1 to 9. Eighteen patients (62 per cent) died of the disease; the increase in mortality rate over that for patients having tumors classified as grade 1 or 2 is significant. Histologically, nothing was noted to distinguish the tumors of patients who survived from those of patients who died.

Grade 4.—The remaining 13 fibrosarcomas (about 17 per cent) of the 78 were classified as tumors of grade 4. The tissues were all more cellular than those of tumors of lower grades. In all but 2 of the 13 tumors, however, scattered areas of fibrogenesis were present, and the tumors of this grade also were classed as fibrocellular.

Marked pleomorphism was characteristic of the individual cellular elements of tumors of grade 4. In some tumors rather plump spindle cells could be found; generally, however, the cellular elements were all sizes and shapes, from small round cells, each having little cytoplasm and a dark, dense nucleus, to large tumor giant cells, each having granular cytoplasm, 1 to 5 or more nuclei, and several dark-staining nucleoli. Tumor giant cells were a conspicuous feature, even on low-power examination, when large numbers of them could be seen in most of the tissues. Mitotic figures, both normal and pathologic, were present in great numbers, and a section of average thickness usually contained at least 1 in every oil immersion field.

These features combined to give the tissues of fibrosarcomas, grade 4, a disordered, "wild" or "dirty" appearance (Fig. 5 *a*) in contradistinction to the more or less orderly appearance of the bulk of tumors of lower grades. Newly formed vessels were much in evidence, but the frequent necrotic patches seen in these tissues testified to the rapidity with which they grow. Another manifestation of rapid growth of tissue in tumors of grade 4 was the difference in the character of the "pseudocapsule." Whereas in the tumors of lower grades this compression zone was composed of tightly packed spindle cells and fibers, in the tumors of grade 4 only a suggestion of compression was evident at the periphery, and the cells in the peripheral zone were little different from the cells in the center of the neoplastic mass (Fig. 5 *b*).

In 3 of these 13 cases the condition could not be adequately followed. In 1 case an undetermined number of local recurrences occurred in the stump after amputation, but the final result is not known; the other 2 patients are known to have died but the cause of death is not known; of the remaining 10 patients, 9 had recurrences; 8 of the patients died of the disease, while 2 were alive and well at the time of our study 14 and 11 years, respectively, after their last operation. As in the case of tumors of lower grades, nothing distinctive was noted about the microscopic appearance or gross surgical description of the tumors of patients who died.

Comment.—From the foregoing it is evident that soft-tissue fibrosarcomas can be rather easily classified into 4 relative grades on the basis of their histopathologic appearance, disregarding for the moment any significance that such a classification might have. To grade the tumors, the relative maturity of the neoplastic tissue is noted; fibrosarcomas, grade 1, must bear close resemblance to benign compact fibromas and to normally situated, nonneoplastic fibrous tissue; fibrosarcomas, grade 4, occupy a position as far removed from this picture as microscopic acumen will enable us to identify cell types.

Recurrent or metastatic lesions were not found to advance in grade, and the structure of the parent or primary neoplasm was faithfully reproduced in local

recurrences and in regional lymph nodes. Whereas these tumors typically metastasize by way of the blood stream, and death usually is due to extensive pulmonary metastasis, to cerebral metastasis, or to a combination of the two, metastasis to the regional lymph nodes does occur at times. In 3 of our 78 cases

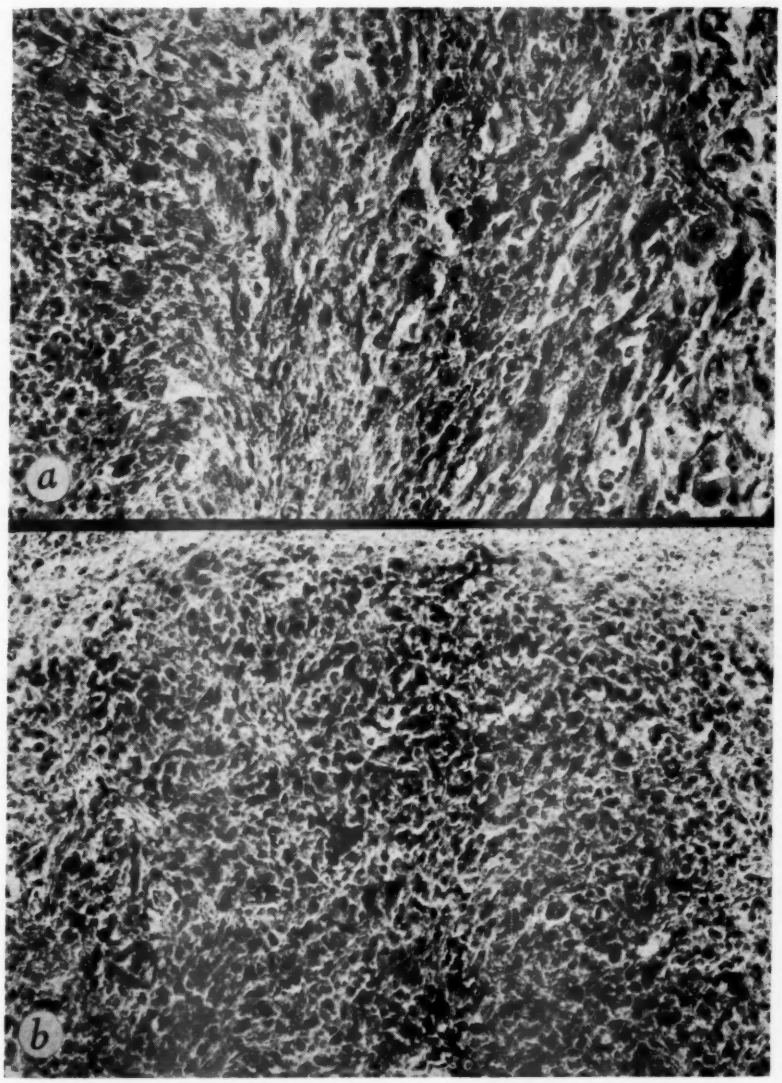


Fig. 5.—Fibrosarcoma, grade 4. *a*, The "wild" disorderly appearance of these high-grade tumors should be noted. Lesion was excised from the left thigh of a man 52 years old, 9 months after onset. No recurrence was noted. Patient was well 14 years later (hematoxylin and eosin, ×100). *b*, High cellularity with negligible production of fibers is evident. The tumor was on the right leg of a man 73 years old. Amputation was done after the third excision for recurrence. Patient died 9 years after amputation; cause unknown (hematoxylin and eosin, ×100).

involvement of regional lymph nodes was proved. In 5 additional cases it seemed clinically certain that metastasis to the regional nodes had occurred. Hence, in this series at least, the true incidence of involvement of lymph nodes would seem to be between 4 and 10 per cent.

TREATMENT AND RESULTS

It is generally agreed that the treatment for fibrosarcoma is unsatisfactory. Just how unsatisfactory it is is difficult to judge by perusing reports in the literature. This is due to several factors: The passing years have changed diagnostic concepts and limited the value of previous reports. Furthermore, many reports listed as "cured" those patients known to be alive as little as 3 years after surgical treatment, when, as a matter of fact, the present study has shown that local recurrences or metastasis may appear many years after primary treatment. Finally, the lack of clearly defined terms demands greatest restraint in the evaluation of any form of treatment, since what is considered wide, radical, or block excision by one surgeon may be considered conservative by another. In our series of cases so many patients had undergone one or several conservative surgical procedures elsewhere, with or without adjunctive treatment with radium, roentgen rays, lead, or Coley's toxins, that it was again impossible to produce figures to prove that any one particular treatment was superior.

Primary amputation obviously would produce a high rate of cure but it would result in the unnecessary sacrifice of many limbs. Commenting on this, Friedman[11] has said, "The relatively innocent appearance and behavior of many early primary tumors generally misleads the surgeon to undertake conservative procedures which are inadequate."

Of our group of 78 cases, the condition of 10 patients could not be followed adequately; however, it is known that 4 had local recurrences of the tumor and that the tumor had metastasized to the lymph nodes in an additional case. In addition to these 10 cases, 5 more were excluded from the group in calculating end results: 3 of the 5 patients were known to be well only three months, 1 year, and 4 years, respectively, after the last surgical procedure; both of the other 2 had fibrosarcomas, grade 4, and died of unknown causes 5½ years and 9 years, respectively, after amputation.

In 63 cases (or 81 per cent) the follow-up information was detailed and complete.

In 23 of the 63 cases (38 per cent) the patients were considered cured. The average follow-up period was 10.7 years, with a range of from 6 to 17 years.

Of the 23 patients who were considered cured, only 4 underwent amputation, and in only 1 of the 4 was amputation done primarily. The other 3 patients underwent amputation after 2, 3, and 8 recurrences, respectively. The remaining 19 cured patients had from 1 to 10 local excisions.

In 40 cases (66 per cent), the patients were known to have died of the disease. The average period of survival after the last surgical procedure was 23.3 months, the range being from 2½ months to 84 months. One-half of the patients who died had had amputations; 4 of them had had amputations done primarily. This total of only 5 primary amputations does not permit us to draw conclusions.

Of the 40 patients who later died, 18 had had from 1 to 9 local excisions; in 2 instances intensive roentgen therapy was used after exploration and biopsy. Because of the fact that fully two-thirds of the patients in this series of cases

had had surgical treatment, the adequacy of which is not known, before being seen at the clinic, conclusions could not be drawn as to the efficacy of conservative or radical local excision. Since 63 per cent of the patients who were cured, and 94 per cent of the patients who died, had had 1 local recurrence or more when local excision was the primary treatment, it can be said that local surgical procedures, at least as practiced in our cases, are highly ineffective in preventing local recurrence.

High-voltage roentgen therapy is another potent weapon against malignant disease in general. In this series of cases, 83 per cent of the patients who were considered cured received roentgen therapy, and it was administered in slightly more than 80 per cent of the cases in which death resulted. Generally, such treatment was directed at the operative site and occasionally at regional lymph nodes; it was usually administered during the early postoperative convalescence. The amount given varied widely, from a single treatment to several courses of treatment administered for a period of several months.

Many patients were treated without the benefit of roentgen therapy and, when given, the amount was so variable that conclusions could not be reached concerning its effectiveness. However, it is generally held that such treatment for fibrosarcoma is ineffective.

Regardless of consideration of the histologic structure or the grade of malignancy, in our series 38 per cent of the patients lived 5 or more years and 19 per cent lived more than 10 years after their last surgical treatment.

Without regard to treatment employed, the patient in our series with a tumor of grade 1 had almost 3 times as good a chance of surviving 5 years after operation as the patient with a tumor of grade 4. A progressive decline in survival rates also was noted in relation to advancing pathologic grades (Table I).

TABLE I. SURVIVAL RATES ACCORDING TO THE GRADE OF MALIGNANT DISEASE

	FIVE YEARS OR MORE		TEN YEARS OR MORE	
GRADE	NUMBER OF CASES	PER CENT OF SURVIVAL	NUMBER OF CASES	PER CENT OF SURVIVAL
1	8	57	4	28
2	5	38	2	15
3	8	31	4	15
4	2	20	2	20

SUMMARY AND CONCLUSIONS

A review was made of the case records and pathologic specimens of 78 cases of fibrosarcomas of the soft tissues of the extremities in which treatment had been administered at the Mayo Clinic during the 10-year period from Jan. 1, 1931, to Dec. 31, 1940. The microscopic diagnosis of fibrosarcoma is difficult at times, even in the hands of expert pathologists; in the course of this study 10 cases were found in which the diagnosis erroneously had been fibrosarcoma. Fibrosarcomas generally can be rather easily classified into 4 relative grades of malignancy, according to the method of Broders based on the histopathologic structure of the tumor. This classification has prognostic significance in that a

study of 63 cases, in which complete and detailed follow-up information was available, showed that the 5-year survival rate for patients having grade 1 fibrosarcoma was 57 per cent; for grade 2 fibrosarcoma, 38 per cent; for grade 3 fibrosarcoma, 31 per cent, and for grade 4 fibrosarcoma, 20 per cent. Because amputation was done primarily in so few of these cases it was impossible to determine whether or not local excision or primary amputation was the treatment of choice. Eighty-three per cent of the patients who survived and 80 per cent of the patients who died had received roentgen therapy as adjunctive treatment.

In our cases the 5-year survival rate for patients having fibrosarcoma, regardless of the pathologic grade of the tumor and of the form of treatment employed, was 38 per cent. We found that the survival rate in fibrosarcoma compared favorably with the survival rate in other major malignancies.

Fibrosarcomas of the soft tissues of the extremities can be grouped into 4 grades of relative malignancy based on the histopathologic structure. The grouping of fibrosarcomas into grades of relative malignancy has prognostic significance in that the survival period is inversely proportional to the grade.

It is impossible to arrive at any definite conclusions as to whether amputation or local excision is the primary treatment of choice. It would appear that roentgen therapy, as administered, did not significantly affect the prognosis.

REFERENCES

1. Bennett, G. A.: Malignant Neoplasms Originating in Synovial Tissues (Synoviomata): a Study of Thirty-Two Specimens Registered at the Army Institute of Pathology During the War-Time Period 1941-1945, J. Bone & Joint Surg. **29**: 259-291, 1947.
2. Bick, E. M.: Fibrosarcoma of the Extremities, Ann. Surg. **101**: 759-765, 1935.
3. Bick, E. M.: Fibroblastic Tumor of the Extremities, Arch. Surg. **35**: 841-853, 1937.
4. Bloodgood, J. C.: Diagnosis and Treatment of Border-Line Pathological Lesions, Surg., Gynec. & Obst. **18**: 19-34, 1914.
5. Boyd, William: Surgical Pathology, ed. 6, Philadelphia, 1947, W. B. Saunders Company, pp. 858.
6. Brooks, S. M.: Carcinoma Which Simulates Sarcoma; Study of 110 Specimens From Various Sites, Arch. Path. **36**: 144-157, 1943.
7. Bunnell, Sterling: Surgery of the Hand, Philadelphia, 1944, J. B. Lippincott Company, pp. 734.
8. Carson, W. J.: Trauma and Malignancy, Am. J. Surg. n.s. **59**: 420-428, 1943.
9. Crane, A. R., and Tremblay, R. G.: Myoblastoma (Granular Cell Myoblastoma or Myoblastic Myoma), Am. J. Path. **21**: 357-376, 1945.
10. Ewing, James: Neoplastic Diseases—a Treatise on Tumors, ed. 4, Philadelphia, 1940, W. B. Saunders Company, pp. 1160.
11. Friedman, Milton: The Treatment of Connective Tissue Fibrosarcoma With Surgery and Radium, Bull. Hosp. Joint Dis. **4**: 66-69, 1943.
12. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone (Including the Jaws and Joints), New York, 1936, The American Journal of Cancer, pp. 832.
13. Hudson, O. C.: Intra-uterine Fibrosarcoma of the Foot; Case Report, Am. J. Cancer **26**: 568-570, 1936.
14. Meyerding, H. W., and Shellito, J. G.: Dupuytren's Contracture of the Foot, J. Internat. Coll. Surgeons **11**: 595-603, 1948.
15. Meyerding, H. W., Broders, A. C., and Hargraves, R. L.: Clinical Aspects of Fibrosarcoma of the Soft Tissues of the Extremities, Surg., Gynec. & Obst. **62**: 1010-1019, 1936.
16. Meyerding, H. W., Black, J. R., and Broders, A. C.: The Etiology and Pathology of Dupuytren's Contracture, Surg., Gynec. & Obst. **72**: 582-590, 1941.
17. Musgrove, J. E., and McDonald, J. R.: Extra-abdominal Desmoid Tumors: Their Differential Diagnosis and Treatment, Arch. Path. **45**: 513-540, 1948.
18. Segond, P.: Quoted by Carson.[8]
19. Shore, B. R.: Spontaneous Cure of a Congenital Recurring Connective-Tissue Tumor, Am. J. Cancer **27**: 736-739, 1936.

EXPERIMENTAL EVIDENCE OF FACTORS CONCERNED IN THE EVENTUAL RECOVERY OF STRANGULATED INTESTINE: EFFECTS OF MASSIVE PENICILLIN THERAPY

HAROLD LAUFMAN, M.D., CHICAGO, ILL.

(From the Department of Surgery, Northwestern University Medical School)

NEW observations make us more and more aware that the physiologic disturbances in intestinal strangulation obstruction are extremely complex. Local factors concerning viability alone are numerous[13] and their interdependence makes it difficult to apply strict criteria for viability. The fundamental phenomena responsible for most local and general disturbances are: (1) interference with circulation, and (2) bacterial invasion. We can now modify both of these factors in therapy, but owing to certain secondary features which we will attempt to describe, such modification has definite limitations.

We have previously reported our experimental efforts to deal with the factor of disturbed circulation.[13] In the present report we wish to describe our studies of the second factor, bacterial invasion, particularly as it applies to the eventual recovery of the involved loop.

Some excellent work has been done recently to demonstrate the favorable effects of chemotherapy and antibiotic therapy on survival in intestinal strangulation. Harper and Blain[9] placed penicillin in isolated, closed intestinal loops and found that it protected the animal to a considerable extent from the usual toxic manifestations, and it prolonged life. Later, Blain[2] used penicillin in animals with strangulated lower ileal obstruction and found that such animals lived longer than did the controls without penicillin. Also, he found that resection of gangrenous loops could be delayed up to certain limits with successful results. Sarnoff and Poth[19] prepared animals with Sulfasuxidine and then deprived a large segment of small intestine of its venous drainage. The survival of such segments through vascularized adhesions indicated that lowering the bacterial content of the fecal stream widened the margin of safety in devascularization. More recently H. A. Davis and associates[5] obtained similar results in rabbits with the use of streptomycin. The bowel in these experiments apparently never reached the stage of irreversible autolysis, and, being almost sterile, was able to survive until a new blood supply was formed. We have established recently,[12] as Dragstedt[6] showed previously, that sterile autolysis of the dog's intestine is completely innocuous to the host, provided intestinal continuity is intact. We were able to reduce the bacterial content of devascularized loops sufficiently to permit the complete autolysis of appreciable lengths of intestinal tissue. This occurred without deleterious effect on the animals. A comparable experiment was performed on the liver by Markowitz, Rappaport, and Scott,[14] who found that while ligation of the hepatic artery

Aided by a grant from the Lois C. Grunow Surgical Fund.

Presented in the Forum on Fundamental Surgical Problems before the Clinical Congress of the American College of Surgeons, Chicago, Ill., Oct. 17 to 21, 1949.

Received for publication, Dec. 19, 1949.

invariably results in liver necrosis and death, the administration of massive doses of penicillin prevented death in such animals.

In the course of strangulation experiments of many types over the past several years we have been impressed by the fact that the microscopic changes in so-called "nonviable" strangulated bowel do not always appear irreversible until a very late stage of autolysis, although the gross appearance may be that of irreversible infarction.[11] We felt that if the ill effects resulting from the action of saprophytic invasion on dead tissue could be suspended until new or collateral circulation formed, or until the original channels became re-established, the host animal should survive the immediate effects. Further, if the absorption of harmful enzymes[20] could be suspended during this period, the limitations to such therapy would logically depend on the degree of eventual recovery and the functional importance of the organ involved. We wished to make practical application of the information at hand to determine to what extent a released strangulated loop which was grossly nonviable could be salvaged without resection and what the eventual effects would be on the animal.

Our preliminary experiments were concerned with standardizing the time factor and the length of loop for strangulation. We found it convenient to subject a 6 to 8 inch segment of lower ileum to venous strangulation with binding tape for approximately 4 to 6 hours. Strangulation of longer loops caused sufficient fluid loss to require replacement therapy. Shorter loops usually ruptured either during this period of time or after release. The medium length loops employed by us remained nonviable by the usual criteria of viability after release of the strangulation, while the experiment was not complicated by extraordinary fluid loss or perforation during the period of strangulation. Nonetheless, such animals invariably died within 24 to 72 hours after release of the strangulation.[13] Postmortem examinations revealed a putrid peritonitis and a gangrenous loop of bowel with or without perforation. Using 10 of these animals as a control group we wished to determine to what extent alteration of the bacterial factor would affect the recoverability of replaced "nonviable" loops.

EXPERIMENTAL DATA

In 10 unprepared dogs weighing approximately 10 kg., a 6 to 8 inch segment of lower ileum, just proximal to the termination of the marginal vein, was strangulated with binding tape applied only snugly enough to obstruct the venous return. This produced a loop which paralleled the usual clinical variety of venous-type strangulation. The strangulated loop was then returned to the abdomen and the abdominal wall closed. Intravenous Nembutal anesthesia was used for surgery. After 6 hours the abdomen was reopened, the strangulating tape was removed, and the segment was observed for viability. In each instance the released loop remained black or dark blue, immobile, and moderately distended, and the involved hemorrhagic mesentery contained no pulsations. The usual resuscitative measures[13] had no effect on the appearance of the loop or on its surface temperature. (By previous experience such a loop would be considered nonviable and, if replaced, would invariably cause the death of the

animal within 24 to 72 hours.) Microscopic sections of bowel at this stage revealed a severe degree of hemorrhage into the various layers, but cellular destruction had not occurred. The loop was then wrapped in omentum and returned to the abdomen and the abdominal wall was closed. Each animal received an intramuscular injection of 300,000 units of penicillin in a 96 hour base. This dose was repeated 96 hours later.

Most of the animals were quite ill for 3 or 4 days, refused to eat, appeared lethargic, and presented a distended abdomen. No other therapy was given. However, each animal survived the immediate postoperative period and within a week each was taking food in small amounts.

The animals were sacrificed at varying periods of time postoperatively, except for 2 animals which died on the fifteenth and nineteenth postoperative days, respectively. The specimens were studied grossly and microscopically.

Our findings revealed changes in the recovering loop which illustrated the limitations to which it is feasible to return loops of questionable viability to the abdomen. It was of interest to note that most of our findings have their counterpart in human cases previously reported in the literature.

Disturbance in Peristaltic Gradient.—Within the first several days postoperatively the nonfunctioning loop did not take part in the natural peristaltic activity. For example, in 1 animal sacrificed at 6 days there was a hard, dry, fecal impaction in the lumen of the involved loop. Ordinarily the luminal contents of the ileum are liquid or semiliquid. The impaction illustrated the inability of the involved loop to move its contents onward. Thus, although the loop was in the process of regaining a blood supply, it was not able to partake in the process of peristalsis.

Several cases of this nature have been reported. Moore,[15] in 1941, reported a case of mesenteric occlusion in which the collateral circulation was sufficient to allow the bowel to recover but not sufficient to allow normal function to continue. Following a lateral anastomosis his patient made a complete recovery. Similar cases were previously reported by Councilman,[3] Reich,[18] and B. B. Davis[4] in connection with mesenteric vascular occlusion. Raw[17] used the term "physiological stricture" to describe the interference with the peristaltic wave as it reaches the recent site of strangulation and he presented a case history to illustrate this condition.

Stenosis of the Involved Loop.—In all of the animals examined after 7 days there was a variable degree of thickening of the bowel wall and narrowing of the lumen in the replaced loop. Stenosis or stricture, with or without intestinal obstruction, following the replacement of a loop of questionable viability in the human being has been reported many times. Barry[1] recently reported 3 cases and Raw[17] 3 others. Grisell[8] reported a case of stenosis following the revival of a borderline segment of bowel by a vasodilating drug. Other cases have been known since the eighteenth century, according to Raw. Garré,[7] in 1892, described a case which stimulated great interest in this condition, and since that time the condition has been known in Germany as "the intestinal stenosis of Garré." The condition has been reproduced in animals by Wangensteen,[22] who

devascularized a 15 inch segment of bowel in the dog and wrapped omentum around it. The result after 72 days was a marked stenosis of the segment.

Constriction Rings.—In 2 instances the involved loop itself was not appreciably narrowed, though its walls were thickened. In these animals, however, there was a marked constriction ring at the sites of the occlusive band. Thompson[21] reported a case of advanced intestinal obstruction in a patient whom he saw 12 weeks after an operation for strangulated hernia. Operation revealed a loop of bowel containing 2 fibrous strictures which represented the constriction rings of the original strangulated hernia.

Plastic Adhesive Peritonitis.—In all of our animals there was a massive formation of adhesions between neighboring loops and the involved area. In several instances the kinking of either the involved loop or adherent loops was so marked that varying degrees of obstruction were present proximal to this area. The 2 mortalities in our series were due to this type of secondary obstruction. Many cases of secondary obstruction due to plastic adhesions following the reduction of a hernia have been reported. Barry[1] has labelled this type of late intestinal obstruction the extrinsic type, in which only the serous layer is involved as a result of plastic peritonitis, in contradistinction to the intrinsic type which is due to the fibrous stenosis previously described.

Intussusception.—In 3 of our animals there was a partial intussusception of the involved segment distally. It is known that the intestine of the dog is more prone to intussusception than is that of the human being. Nonetheless, the fact that it occurred indicates that intussusception is a potential source of secondary complicaions. In one of our previous reports[13] we observed 2 instances in which viable bowel was returned to the abdomen only to have the animals die several days later of strangulated intussusception of the involved segment. We know of no report of this condition occurring in the human being after strangulation.

TABLE I. REPLACEMENT OF STRANGULATED INTESTINAL LOOPS IN ANIMALS TREATED WITH MASSIVE PENICILLIN THERAPY

DOG NUMBER*	DURATION OF VENOUS-TYPE STRANGULATION OF 6 TO 8 IN. OF ILEUM (HOURS)	DISPOSITION	FINDINGS
11	5	Sacrificed 35 days	Mild stenosis; constriction rings; adhesions
12	6	Sacrificed 6 days	Hard dry fecal impaction in lumen of involved loop
13	4½	Sacrificed 7 days	Mild adhesions; partial intussusception
14	5	Sacrificed 21 days	Severe adhesions; incomplete obstruction; partial intussusception
15	4½	Sacrificed 42 days	Mild stenosis; marked adhesions
16	4	Died 15 days P.O.	Severe adhesions; secondary obstruction
17	5½	Sacrificed 35 days	Thickened walls; constriction rings; adhesions
18	6	Sacrificed 28 days	Severe stenosis with thickened bowel wall; adhesions
19	5	Died 19 days P.O.	Severe adhesions; secondary obstruction
20	5½	Sacrificed 14 days	Mild stenosis; moderate adhesions; partial intussusception

*Ten control dogs not treated with penicillin; all died within 72 hours (see text).

DISCUSSION

Our experiments indicate that massive penicillin therapy widens the margin of safety when a strangulated loop is returned to the abdominal cavity. However, the experiments also suggest that dependence upon antibiotics in extremely borderline cases may result in a high percentage of poststrangulation complications which are commensurate with the degree of tissue destruction.

Despite the unquestionable value of massive antibiotic therapy in strangulation obstruction, a loop of bowel which does not respond to resuscitative measures should probably not be replaced. We have found that there is a stage in the process of hemorrhagic infarction during which the bowel no longer responds to resuscitative measures, and is, therefore, declared "nonviable," but in which stage the cells of the mural structures have not yet undergone irreversible damage. Beyond this stage antibiotics cannot be expected to be of predictable value. Since it is almost impossible to delineate this stage clinically from frank infarction, it is undoubtedly more advisable to resect such a segment rather than depend upon the antibiotics. Penicillin will not revive gangrenous tissue.

The incidence of complications previously reported in the literature following the replacement of strangulated loops in human beings is quite low. Most of these cases were reported before the advent of antibiotics and very few borderline cases, treated without resection, survived. Thus, the incidence of poststrangulation complications as we have described them was also quite rare.

The control of the destructive influence of the bacterial factor in strangulation obstruction may occur in one of several ways. (1) Upon release of a strangulation, if the diminished blood supply is sufficient to oxygenate the tissues, and the bacterial invasion has not been overwhelming, recovery may be spontaneous. (2) The blood supply to an involved segment after release of a strangulation may be improved by releasing residual spasm in the vessels of the segment by resuscitative measures. (3) Control of the bacterial invasion itself may be accomplished within certain limits by antibiotics. The bacterial and circulatory factors are interdependent. If the bacterial invasion is controlled, recovery must of necessity depend upon the degree of destruction. The greater the destruction of tissue the longer is the pathway to recovery. If antibiotics are depended upon to bring about recovery of tissues which have undergone an extreme degree of destruction, the functional capacity of the organ will be impaired accordingly. Our experiments indicate that such impairment of function in the intestine might lead to dire consequences.

The usual type of venous strangulation results in the stages of venous engorgement, hemorrhagic infiltration of tissue, spasm of arteries, thrombosis of vessels, and actual necrosis. Necrosis of mucosa may result in sloughs of considerable size. These areas may be completely restored eventually due to the remarkable regenerative power of the mucosa. If destruction is severe enough, healing by scar tissue takes place. It would appear from the examination of our material that the greater the blood extravasation into the tissues of the

intestinal wall the more severe is the fibrous thickening. This occurs mainly in the submucosal layer. When antibiotics are used they reach the intestinal tissues by way of diminished blood supply, but are able under certain circumstances to limit bacterial invasion sufficiently to interrupt the process of destruction and maintain anatomic integrity of the intestinal wall until adequate blood supply can be obtained to promote healing. The ill effects of the healing process appear to be directly related to the degree of destruction wrought by the extravasation of blood cells, the anoxia, and the bacterial invasion.

SUMMARY

Massive doses of penicillin will apparently widen the margin of safety in the replacement of strangulated intestinal loops of questionable viability. Antibiotics can be depended upon only if frank death of tissue has not occurred. The high percentage of complications resulting from the borderline survival of greatly damaged intestinal tissue is the most important drawback to the replacement of such loops even when penicillin is used. We feel, therefore, that released strangulated loops of highly questionable viability should still be resected if the surgeon is at all concerned about the recoverability of the tissue. Some of the factors involved in the eventual recovery of strangulated intestine are described.

REFERENCES

1. Barry, H. C.: Fibrous Stricture of the Small Intestine Following Strangulated Hernia, Brit. J. Surg. **30**: 64-69, 1942.
2. Blain, A.: Penicillin in Experimental Intestinal Obstruction, Surg., Gynec. & Obst. **84**: 753-758, 1947.
3. Councilman, W. T.: Three Cases of Occlusion of the Superior Mesenteric Artery, Boston M. & S. J. **130**: 410, 1894.
4. Davis, B. B.: Thrombosis and Embolism of the Mesenteric Vessels, Nebraska M. J. **6**: 101, 1921.
5. Davis, H. A., Gaster, J., Marsh, R. L., and Pritel, P. A.: The Effect of Streptomycin in Experimental Strangulation of the Bowel, Surg., Gynec. & Obst. **87**: 63-67, 1948.
6. Dragstedt, L. R., Dragstedt, C. A., McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials From the Intestine, J. Exper. Med. **30**: 109, 1919.
7. Garré, C.: Ueber eine eigenartige Form von narbigen Darmstenose nach Brucheinklemmung, Beitr. z. klin. Chir. **9**: 187, 1892.
8. Grisell, T. L.: Complications in Treatment of Incarcerated Hernia With Vasodilatant Drug, J. Indiana M. A. **42**: 522-524, 1949.
9. Harper, W. H., and Blain, A.: The Effect of Penicillin in Experimental Intestinal Obstruction, Bull. Johns Hopkins Hosp. **76**: 221-244, 1945.
10. Interim Report of Surgical Subcommittee of the Clinical Research Committee of the Public Health Department of the London County Council: Viability of Strangulated Bowel, Brit. M. J. **116**: 43-46, 1948.
11. Laufman, H.: Occlusion of the Mesenteric Blood Vessels and Associated Phenomena, Thesis, Northwestern University Library, 1942.
12. Laufman, H., Martin, W. B., Method, H., Tuell, S. W., and Harding, H.: Observations in Strangulation Obstruction: II. The Fate of Sterile Devascularized Intestine in the Peritoneal Cavity, Arch. Surg. **59**: 550-564, 1949.
13. Laufman, H., and Method, H.: The Role of Vascular Spasm in Recovery of Strangulated Intestine, Surg., Gynec., & Obst. **85**: 675-686, 1947.
14. Markowitz, J., Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**: 305, 1949.
15. Moore, T.: Mesenteric Vascular Occlusion, Brit. J. Surg. **28**: 347, 1941.
16. Noer, R. J., and Derr, J. W.: Revascularization Following Experimental Mesenteric Vascular Occlusion, Arch. Surg. **58**: 576-588, 1949.
17. Raw, S. C.: Stricture of Small Bowel Following Strangulated Hernia, Lancet **244**: 460, 1943.

18. Reich, A.: Embolie und Thrombose der Mesenterialgafasse, Ergebn. d. Chir. u. Orthop. **7**: 515, 1913.
19. Sarnoff, S. J., and Poth, E. J.: Intestinal Obstruction: I. The Protective Action of Succinylsulfathiazole Following Simple Venous Occlusion, SURGERY **16**: 927-931, 1944.
20. Tanturi, C. A., and Anderson, R. E.: Morbid Factors in Experimental Appendicitis, Surg., Gynec. & Obst. **89**: 165-180, 1949.
21. Thompson, A.: Brit. M. J. **2**: 950, 1897. Quoted by Barry.[1]
22. Wangensteen, O. H.: Intestinal Obstructions: A Physiological and Clinical Consideration With Emphasis on Therapy, Including Description of Operative Procedures, ed. 2, Springfield, Ill., 1942, Charles C Thomas, Publisher, p. 292.

THE TREATMENT OF STAPHYLOCOCCIC MENINGITIS

With a Review of the Literature and With Particular Reference to the Results With Bacitracin: A Report of Five Cases

Paul Teng, M.D., and Frank L. Meleney, M.D., New York, N. Y.

(From the Laboratory for Bacteriological Research of the Department of Surgery, Columbia University College of Physicians and Surgeons)

STAPHYLOCOCCIC meningitis is relatively uncommon. In the literature, with the exception of single case reports, it is usually included under the title of purulent or septic meningitis. The most frequent causative organisms, in the order listed by Neal in 1924 in a review of 1,535 cases, are: meningococcus, pneumococcus, streptococcus, *Haemophilus influenzae,* staphylococcus, and *Bacillus coli.* Staphylococcus was found in only eleven cases in this series.[1]

Prior to the discovery of the sulfonamides and penicillin, staphylococcic meningitis was usually a fatal disease. Rare instances of recovery were reported. A review of the old textbooks reveals that the following statements have been made with regard to this disease. Griffith mentioned that in patients with staphylococcic meningitis the illness runs "a short course and the prognosis is almost entirely unfavorable."[2] Porter and Carter remarked that, "In staphylococcic meningitis, treatment is essentially symptomatic and invariably useless."[3] Neal, in Tice's *Practice of Medicine,* concluded that, "The prognosis of cases of purulent meningitis due to organisms other than the meningococcus is bad but not absolutely hopeless."[4] Grinker stated that "The majority of cases die after a period of days or weeks. We hear of occasional complete recoveries, but most of these are of doubtful authenticity." He wrote that the survivals had possibly been patients with cases of serous meningitis, of meningeal irritation, or of a localized form of purulent meningitis which is amenable to surgical treatment after the deposits of pus have been thoroughly evacuated.[5] Ballenger, in 1930, reported one instance of recovery and stated that the majority of the survival cases recorded in the literature were of the localized type.[6] Schless, in 1932, after a review of the literature, summarized that generalized or disseminated staphylococcic meningitis of hematogenous origin with distinct spinal fluid responses of a positive culture of *Staphylococcus aureus* is invariably fatal, and "No recovery has been reported."[7] In this paper, however, he presented one case of survival.

Since staphylococcic meningitis is rare, individual experience with this disease is limited. Sporadically, more or less as a curiosity, a recovery has been described in the literature. Few fatal cases were reported because it seemed to be taken for granted that death was the expected outcome. In 1943, MacNeal and associates entitled their article "Staphylococcic Meningitis From Hip-

This study was supported in part by a grant from the Medical Research and Development Board of the Office of the Surgeon General of the Army.

The Bacitracin used was supplied by the Commercial Solvents Corporation of Terre Haute, Indiana.

Received for publication, Nov. 10, 1949.

pocrates to LeGendre and Beaussenat: A Mortal Disease.''[8] They also reported in another article the largest personal series of staphylococcic meningitis cases recorded in the medical literature.[9] In ten years' time, they successfully treated eleven patients with bacteriophage, but they, too, reported only recoveries and neglected to mention how many failed to respond to bacteriophage. From 1897 to 1912, a period of sixteen years, fifty-seven patients with septic meningitis were treated by Day. Three patients recovered. In this series, his two patients with staphylococcic meningitis failed to recover.[10] In 1924, Dandy in his article on the treatment of staphylococcic and streptococcic meningitis made a rough estimate of the mortality rate of all types of septic meningitis and said, ''At best, the mortality of all varieties of septic meningitis is excessively high. It will surely run well over 90 per cent and in many forms will probably be over 95 per cent.''[11] There are no more exact figures of the mortality rate from staphylococcic meningitis either before or since the era of chemotherapy.

THE PORTAL OF ENTRY FOR THE ORGANISMS

Bacteria may reach the meninges by three major routes, namely, (a) by way of the arterial blood; (b) by way of the adjacent tissues, which include an infected middle ear or mastoid, an infected paranasal sinus, a septic thrombosed blood sinus of the dura, osteomyelitis of the skull or spine, an epidural or intracerebral or intracerebellar abscess; (c) by direct implantation, as in compound fracture of the skull or contamination during an operation on the central nervous system. There can be no doubt that the most frequent route is by direct implantation of the organisms in the subarachnoid space in compound fractures of the cranium. In extremely rare cases, meningitis may follow an infected congenital sacral sinus[12] or a meningocele.

The cerebrospinal fluid is almost defenseless against infection. It contains a minimal amount of any kind of bacterial antibody, but has enough protein and carbohydrate for the growth of the bacteria. Once the infection reaches the subarachnoid space, it is rapidly spread through the cerebrospinal fluid. For this reason, septic meningitis of hematogenous origin is more fatal than that which spreads from infected adjacent tissues. In the latter, it is possible for adhesions to be laid down inside of the dura before infection has eroded through. After infection has spread over the surface of the brain, the cortex is exposed to the bacterial toxin which poisons the delicate nerve cells, and this probably accounts for the acuteness and seriousness of the disease.

TREATMENT

The old methods of treating purulent meningitis before the discovery of the sulfonamides and the antibiotics are of interest. The following gives a brief historical review of the treatment of the disease.

Surgical Treatment.—It is probable that the surgeons have more of an opportunity to observe staphylococcic or streptococcic meningitis than do the internists, because these infections often follow a compound fracture of the skull, a brain abscess, or contamination of operations on the central nervous system, or are secondary to an infected middle ear, mastoid, sinus, or some

other head organ. Meningitis has been considered by some surgeons to be an encased abscess of the cerebrospinal space, therefore, *ipso facto*, demanding open drainage.

Percivall Pott in 1760 first recognized the "putrefaction of the membranes" following skull fracture, one full century before the knowledge of bacterial infection. He considered this as a grave condition and strongly advocated the routine exposure and drainage of all fracture wounds of the skull as a preventive measure.[13] Nevertheless, his teaching was rarely followed. The name meningitis was introduced in the literature by Herpin in 1803.[14] It was not until 1873 that Gross, after experience in treating wounds of the head during the American Civil War, strongly stated that the "necessity for operation is not to be questioned."[15] Galippe,[16] in 1889, seems to have been the first to demonstrate that the staphylococcus is one of the causative agents of meningitis.

When the bacterial origin of infection became known, Victor Horsley, in 1890, reported two cases of septic meningitis; he had treated these patients surgically.[17] Considering the infected subarachnoid space an encased abscess, he applied the principle of drainage to the cerebrospinal space. He treated one of his patients by continuous drainage of the spinal canal after laminectomy and the other by cisterna magna-lumbar spinal irrigation with his favorite antiseptic, bichloride of mercury. His two patients did not survive. He described his treatment in the following words: "I have put down septic meningitis as a condition which might be improved by operation, such as free drainage and irrigation with warm disinfectants. I do not, however, believe that this course will always successfully rescue otherwise hopeless cases. In fact, I have operated twice, once by way of exploration and once deliberately, but in both the moribund patients succumbed, after temporary though marked remission of their symptoms." He suggested using the same procedure in tuberculous meningitis. He hoped "that the good results obtained in tubercular peritonitis by draining the peritoneal cavity might not improbably be secured in meningitis, if trephining were similarly resorted to," but he did not have the opportunity to try this method.

Haynes, in 1912, in his article on the surgical treatment of septe meningitis, definitely stated that "Septic conditions are usually surgical opportunities and demand surgical treatment."[18] He widened the foramen magnum by partial removal of the occipital bone to secure a drainage from the cisterna magna. One year later, Day[19] tried this same method, modified, in eight cases of septic meningitis, and Dench[20] used it on three patients, but without success. Day ended his report with these words, "Despite the none too encouraging result of the past, the curative treatment of otitic meningitis is only a matter of time. Just as in aviation, the course will be marked by a long line of failures and many fatalities before success is achieved."[19]

In 1924, Dandy reviewed the surgical treatment of septic meningitis and listed three types of procedures: (a) intermittent drainage by repeated lumbar punctures; (b) continuous drainage from the spinal canal, cisterna magna, pontine cisterna, lateral ventricles, or the subarachnoid space in the parietal region; (c) irrigations of the subarachnoid space by bland or antiseptic solu-

tions. Dandy modified the Haynes operation by the insertion of the funnel end of a catheter into the cisterna magna for drainage. He tried it in one case of staphylococcic meningitis and the patient survived. He thought that this drainage would probably work better in staphylococcic and streptococcic meningitis than in the pneumococcic type. Thus, he wrote, "I have restricted the application of cisternal drainage to staphylococcus and streptococcus infections in which the cerebrospinal fluid is not sufficiently altered in consistency to militate against drainage."[11] From 1893 to 1938 twenty cases were reported as cured by drainage of the cerebrospinal fluid.[21]

Solutions and antiseptics used with the surgical treatment of meningitis, either by way of lumbar puncture or to irrigate the cerebrospinal space, have been bichloride of mercury,[17] Lysol,[22] and protargol,[23, 24] as well as plain normal saline solution. Other drugs and dyes that have been injected into the spinal canal or ventricle are colloid tin,[25] Urotropin,[10] oxycyanide of mercury,[10] and methylrosanilin (gentian violet).[26] As a result of this kind of treatment, only one case of staphylococcic meningitis was reported as cured, and that by the intraventricular injection of gentian violet.[26]

Treatment With Staphylococcus Vaccine.—Lortat-Jacob and Grivot, in 1920, reported the use of staphylococcal vaccine in addition to drainage of the subarachnoid space by repeated lumbar puncture, but the role played by the vaccine is doubtful.[27]

Treatment With Staphylococcus Bacteriophage.—Schless, in 1932,[7] Dunlop, in 1935,[28] Frank, in 1936,[29] and MacNeal and co-workers, in 1943,[9] all described the use of bacteriophage in the treatment of the staphylococcal type of cerebrospinal fever. The latter authors reported eleven cases of recovery, seven of generalized and four of localized staphylococcic meningitis.

Treatment With the Sulfonamides.—When sulfanilamide, sulfathiazole, and sulfadiazine were used as therapeutic agents, the situation began to brighten still further. Up to July of 1948 at least fifteen cases of recovery were added to the literature[21] (Table I). However, the application of the sulfonamides to the central nervous system was found to be unsafe. Pilcher demonstrated that sulfanilamide, sulfathiazole, and sulfadiazine were all invariably irritating.[30] These drugs produced marked irritative and destructive effects in the brain tissue and its coverings. Acute leptomeningitis, meningeal fibrosis, subcortical bleeding, gliosis, microglial metamorphosis, and the degeneration of neurones were the most striking changes. Of these, sulfathiazole caused the most and sulfanilamide the least irritation. However, sulfanilamide is seldom effective against staphylococci. In spite of their injury to the central nervous system and the now extensive use of penicillin, the sulfonamides are still occasionally resorted to in the treatment of patients with staphylococcic meningitis, particularly when the causative strain is resistant to penicillin.

Treatment With Penicillin.—Since penicillin has become available, the situation has greatly improved. A greater number of recoveries have been recorded (see Table I). At this point we would like to consider the possible routes by which penicillin may be administered in the treatment of staphylococcic meningitis.

TABLE I. CASES OF RECOVERY FROM STAPHYLOCOCCIC MENINGITIS REPORTED FROM 1941 TO 1948

YEAR	AUTHOR	CEREBROSPINAL FLUID, CULTURES, AND CELL COUNT (WHEN KNOWN)	SOURCE OF INFECTION (WHEN KNOWN) AND TREATMENT
1941	Roberts[50]	Ventricular fluid, 25,000 cells; spinal fluid, 13,000 cells; *Haemophilus influenzae* and *Staph. aureus*	Sulfadiazine and sulfathiazole
1941	Hoyne[51]	Spinal fluid, 750 cells *Staphylococcus albus* in cerebrospinal fluid and blood cultures	Staphylococcus antitoxin and sulfanilamide
1941	Hoyne[51]	Spinal fluid, 120 cells *Staph. albus* in cerebrospinal fluid and blood cultures	Sulfanilamide
1941	Hoyne[51]	Spinal fluid, 2,500 cells hemolytic *Staph. aureus* in cerebrospinal fluid and blood cultures	Sulfanilamide
1941	Hoyne[51]	Spinal fluid, 730 cells *Staph. albus* in cerebrospinal fluid and blood cultures	Sulfathiazole
1942	Peters, et al.[52]	Spinal fluid, 3,444 cells *Staph. aureus*	Sulfadiazine
1942	McCune[53]	Spinal fluid, 1,233 cells *Staph. aureus*	Otitis media; sulfadiazine
1942	Huber and Nouvail[54]	Spinal fluid, 5,000 cells *Staph. aureus*	War wound of skull; sulfathiazole
1943	Aversa[55]	Spinal fluid, 456 cells *Staph. aureus*	Cavernous sinus thrombosis; sulfapyridine and sulfathiazole
1943	MacNeal, et al.[9]	Spinal fluid, 1,600 cells *Staph. aureus* nonhemolytic	Fracture of skull; bacteriophage
1943	MacNeal, et al.[9]	Spinal fluid, 598 cells *Staph. aureus*	Infected craniotomy wound; bacteriophage
1943	MacNeal, et al.[9]	*Staphylococcus citreus* and *Staph. albus* both in cerebrospinal fluid and blood cultures	Bacteriophage
1943	MacNeal, et al.[9]	Spinal fluid, 2,875 cells *Staph. aureus* in cerebrospinal fluid and blood cultures	After pneumonia; bacteriophage
1943	MacNeal, et al.[9]	Spinal fluid, 6,000 cells *Staph. aureus*	Infected craniotomy wound; bacteriophage
1943	MacNeal, et al.[9]	*Staph. aureus* in blood and cerebrospinal fluid cultures	Cavernous sinus thrombosis; Azosulfamide and bacteriophage
1943	Tolan[56]	Spinal fluid, 8,900 cells *Staphylococcus hemolyticus*	Mastoiditis; sulfadiazine
1944	Brash[57]	Spinal fluid, thick pus *Staph. aureus*	Sulfadiazine and sulfathiazole
1944	Evans[58]	*Staph. aureus*	Infected laminectomy wound; penicillin, 5,000 units by intrathecal injection
1944	Evans[58]	Spinal fluid, 4,100 cells *Staph. aureus*	Frontal sinusitis, brain abscess; penicillin, intrathecal and into abscess cavity

TABLE I.—CONT'D

YEAR	AUTHOR	CEREBROSPINAL FLUID, CULTURES, AND CELL COUNT (WHEN KNOWN)	SOURCE OF INFECTION (WHEN KNOWN) AND TREATMENT
1944	McCune and Evans[59]	Spinal fluid, 23,750 cells *Staph. aureus*	Fracture of base of skull; penicillin, intrathecal
1944	McCollum[60]	Spinal fluid, 5,600 cells *Staph. aureus*	Otitis media; penicillin, intrathecal
1945	Worth[61]	Spinal fluid, 12,000 cells *Staph. aureus*	Osteomyelitis of spine; penicillin, intracisternal
1945	Johnson and Walker[40]	*Staph. albus* in ventricular fluid	Otitis media; penicillin by intraventricular injections, 15,000 to 50,000 units
1945	Gaumond and Grandbois[62]	Spinal fluid, 940 cells *Staph. aureus*, nonhemolytic both in blood and cerebrospinal cultures	Cellulitis of face, cavernous sinus thrombosis; penicillin, intrathecal
1945	Amyot[63]	Spinal fluid, purulent *Staph. aureus*	Cellulitis, lumbo-abdominal region; penicillin, intrathecal
1945	Clemens[64]	Spinal fluid, 952 cells *Staph. albus* hemolytic in blood and cerebrospinal fluid cultures	Hematogenous; sulfadiazine and sulfathiazole
1946	Erickson, et al.[37]	No detail *Staph. aureus*	Cerebral abscess; penicillin
1946	Naffziger, et al.[65]	No detail *Staph. aureus*	Infected laminectomy wound; penicillin
1946	Hjertaas[66]	No detail *Staph. aureus*	Fracture of skull; penicillin
1946	Wyke and Vanderfield[67]	Spinal fluid, 1,100 cells *Staph. aureus*	Otitis media, cerebral abscess; penicillin by intraventricular injection
1946	Hall, et al.[68]	No detail Staphylococcus	Hematogenous (?): penicillin and sulfadiazine
1946	Hall, et al.[68]	No detail Staphylococcus	Penicillin and sulfadiazine
1946	Miller and Delohery[69]	Spinal fluid, 7,400 cells Ventricular fluid, 1,780 cells *Staph. aureus* hemolytic	Gunshot wound of head; penicillin, 30,000 units intrathecally, 50,000 to 100,000 units by intraventricular injection
1948	Hoyne and Brown[70]	Spinal fluid, 1 200 cells *Staph. aureus* hemolytic in cerebrospinal fluid and blood cultures	Abrasion wound of scalp; sulfathiazole by mouth, penicillin intramuscularly
1948	Hoyne and Brown[70]	No detail *Staph. aureus*	Sulfadiazine
1948	Hoyne and Brown[70]	No detail *Staph. aureus*	Sulfadiazine
1948	Hoyne and Brown[70]	No detail *Staph. albus*	Penicillin intramuscularly and sulfonamide
1948	Hoyne and Brown[70]	No detail *Staph. aureus*	Penicillin intramuscularly and sulfonamide
1948	Hoyne and Brown[70]	No detail *Staph. aureus*	Penicillin intramuscularly and sulfonamide
1948	Hoyne and Brown[70]	No detail *Staph. aureus* hemolytic in blood and cerebrospinal fluid cultures	Penicillin intramuscularly and intrathecally, sulfonamide

(*Continued on following page.*)

TABLE I.—CONT'D

YEAR	AUTHOR	CEREBROSPINAL FLUID, CULTURES, AND CELL COUNT (WHEN KNOWN)	SOURCE OF INFECTION (WHEN KNOWN) AND TREATMENT
1949	Teng and Meleney	Ventricular cerebrospinal fluid culture; hemolytic *Staph. aureus*	Compound fracture; penicillin intramuscularly and intraventricularly and sulfadiazine failed; bacitracin intraventricularly and intramuscularly successful
1949	Teng and Meleney	Spinal fluid, 1,500 cells, coagulase-positive staphylococcus in lumbar cerebrospinal fluid and subdural abscess	Postoperative for tumor; penicillin, streptomycin, and sulfonamides failed; drainage of abscess with bacitracin locally, intrathecally, and intramuscularly successful
1949	Teng and Meleney	*Staph. albus* in subdural abscess	Postoperative topectomy; penicillin failed; bacitracin locally and intramuscularly successful
1949	Teng and Meleney	Spinal fluid, 7,300 cells, coagulase-positive hemolytic *Staph. aureus* in cerebrospinal fluid	Hematogenous (?); no response to intramuscular and intrathecal penicillin or streptomycin or to sulfadiazine or aureomycin; bacitracin intrathecally and intramuscularly successful
1949	Teng and Meleney	Spinal fluid, 32,000 cells, hemolytic *Staph. aureus* in cerebrospinal fluid	Hematogenous; penicillin intramuscularly and intraventricularly and sulfadiazine failed; bacitracin intrathecally and intraventricularly successful

1. Intravenous or Intramuscular Injection. Neither the intravenous nor the intramuscular injection of penicillin can reach the cerebrospinal fluid in significant concentration,[31, 32] even in the presence of meningitis.[33] Schwemlein and his associates demonstrated that by continuous intravenous drip of 10 to 25 million units of penicillin for twenty-four hours in 162 patients with normal meninges, 0.03 to 0.21 unit of the drug was found per c.c. in the spinal fluid.[34] However, these levels were not considered high enough to control staphylococcic meningitis.

2. Intrathecal Injection. This is the effective route of instilling penicillin in the treatment of meningitis, but it is necessary for the dosage to be carefully adjusted. Walker and Johnson demonstrated in the monkey that 20,000 units injected into the lumbar subarachnoid space induced epileptic attacks, coma, and death within twelve hours.[35] In man, this dosage of penicillin by intrathecal injection can be well tolerated, but Walker and Johnson have reported that 100,000 units of penicillin injected intrathecally in 5 c.c. of saline solution caused retention of urine, paresthesia, and unsteady gait in a man.[35] Repeated doses of smaller amounts have frequently caused radiculitis, arachnoiditis, paralysis, and paraplegia.[35-37]

3. Intracisternal Injection. When there is an obstruction or a block in the spinal subarachnoid space, penicillin may be given by the intracisternal route, but the dosage should be even more cautiously determined. In the monkey, 10,000 units given by way of the cisterna magna are enough to produce a fatal epileptic convulsion.[38] In man, Neymann has found that intracisternal injection of 30,000 to 50,000 units of penicillin may induce a status epilepticus with a fatal outcome. He reported two deaths by the injection of 50,000 units of penicillin into the cisterna magna.[39] A dose larger than 10,000 units is not advisable for intracisternal injection.

4. Intraventricular Injection. With ventriculitis and a block of the outflow of the cerebrospinal fluid, penicillin may be instilled directly into the ventricle. The space of the ventricles is not large, the site is more sensitive, and should there be a block in the outflow, a smaller dose of less than 5,000 units tends to remain in the ventricle and maintain an effective level longer than that with a patent outlet. Johnson and Walker warned against the dangers of intraventricular administration of penicillin.[40] They injected 50,000 units of penicillin in 5 c.c. of isotonic saline solution into the lateral ventricle of a boy 22 months of age and produced unconsciousness, a state of collapse, and frequent paroxysmal generalized clonic spasms. However, later injections of 15,000 units in the same patient were tolerated and the patient survived.

COLLECTION OF SURVIVAL CASES OF STAPHYLOCOCCIC MENINGITIS

MacNeal, Frisbee, and Blevins collected forty-eight cases of proved staphylococcic meningitis from 1893 through 1941; all of these patients recovered from this usually fatal disease.[21] We have found forty additional cases recorded in the medical literature from 1941 to June 30, 1948 (see Table I). It is possible that all of the cases reported during this seven and one-half year period have not been included, but this gives us a total of at least eighty-eight recoveries. For about one-half a century before the use of the sulfonamides and penicillin, there were only thirty-nine instances of survival recorded. With the use of the sulfonamides and penicillin, in a little more than a decade, forty-nine cases were reported as cured. The difference is striking and the results are encouraging, but it is obvious that these newer remedies have frequently failed to cure staphylococcic meningitis, so that we cannot be entirely satisfied with the results so far reported. Not only is the action of the sulfonamides limited against staphylococci, but these drugs have a marked toxic effect on the central nervous system. Toxic effects also limit the dosage of penicillin, and as time goes on there are an increasing number of staphylococcal strains which are found to be resistant to penicillin, and in these cases penicillin therapy is ineffective. However, these resistant strains of staphylococci have often been found to be susceptible to the newer antibiotic, bacitracin.[41]

In this paper we will present the results of treatment with bacitracin in five consecutive cases of staphylococcic meningitis which had not responded to penicillin treatment. This will bring the number of reported survivals to at least ninety-three.

BACITRACIN TREATMENT OF STAPHYLOCOCCIC MENINGITIS

As is the case with penicillin, both in normal animals and in patients after parenteral injection, only a trace of bacitracin can be found in the cerebrospinal fluid.[42, 43] In the presence of staphylococcic meningitis in dogs, by intramuscular injection of 10,000 units a much higher concentration of bacitracin could be found in the cerebrospinal fluid. Nevertheless, by intramuscular injection alone we could not save any of our experimental animals.[43]

Intracisternal injection of 10,000 units of bacitracin in 3 c.c. of normal saline solution in dogs of 10 kg. of body weight produced no ill effects except for transient neck rigidity, pleocytosis, and an elevation of body temperature of 1° to 2° F. The subarachnoidal deposition was rapidly excreted in the urine, but twelve hours after the intracisternal injection of 10,000 units, a concentration of 1 unit per cubic centimeter could still be demonstrated in the cerebrospinal fluid.[44] The intraventricular injection of 5,000 units of bacitracin in 0.5 c.c. of physiologic saline solution in cats of from 2.5 to 3.0 kg. of body weight is epileptogenic, but it does not kill the animals and recovery is prompt and complete. Under intravenous Nembutal anesthesia the injection of the same amount of bacitracin produced no convulsions.[44] Five thousand units of bacitracin in powder form, when applied to the cortex of the animal's brain, has produced no convulsions.[45] A similar dosage of penicillin, when applied to or injected into the cortex, regularly produces status epilepticus in cats and monkeys.[46]

In our experiments with hemolytic *Staph. aureus* meningitis in dogs, the intracisternal injection of 5,000 to 10,000 units of bacitracin in 3 to 4 c.c. of normal saline solution one to five and one-half hours after the inoculation of approximately 500 million organisms by the same route, saved 75 per cent of the meningitic animals. Animals treated within three hours after the bacterial inoculation all survived. All control animals died, including two animals in moribund condition which were killed to prevent their further distress. Death usually occurred within six and one-half hours after the intracisternal injection of the organisms.[43] On the basis of these experiments we felt justified in using bacitracin in the treatment of human meningitis by intrathecal and intraventricular as well as by intramuscular injections.

Among the 270 patients with extensive infection treated with bacitracin systemically by intramuscular injection, as recently reported in *Surgery, Gynecology and Obstetrics,* there were four with staphylococcal meningitis.[47] One of these cases was briefly summarized in that report, but the whole group deserves more detailed description and serves as the basis for this report together with a patient more recently treated. In adult patients, we found that 5,000 to 10,000 units of bacitracin in 3 to 5 c.c. of normal saline solution could be injected intrathecally once or twice a day for five to ten days with no untoward effects. Also 3,000 to 10,000 units in 10 c.c. of normal saline solution, injected into the lateral ventricle at twelve-hour intervals, were well tolerated. Furthermore, no ill effects were produced when 5,000 to 10,000 units in 10 c.c. of normal saline solution were applied to a freshly cut cortical surface measur-

ing approximately 6 by 4 by 2.5 cm. in each hemisphere, as a prophylactic measure in cases of topectomies of areas 9 and 10.[44]

Blood serum, pus, or penicillinase produced by gram-negative microorganisms do not inhibit the action of bacitracin.[48] No substance similar to penicillinase has yet been found which inactivates bacitracin, and hypersensitivity to this antibiotic is extremely rare.[47] However, it must be pointed out that some strains of staphylococci are not susceptible to bacitracin.

Certain of the earlier lots of bacitracin manufactured by the deep tank method were found to be irritating to the kidneys following intramuscular injection, but this aspect is minimal with the material most recently manufactured and which is now available. Furthermore, this characteristic of bacitracin in its present state has no deleterious effect on brain tissue.[44, 45]

CASE REPORTS

CASE 1.—G. L. (Bacitracin Study No. 2011), a man 65 years of age, was admitted to the Cincinnati General Hospital on April 15, 1948, and was discharged July 22, 1948. The patient was admitted to the hospital in a stuporous condition. Physical examination revealed a fracture of the base of the skull and a cerebral contusion with an obvious acute and chronic alcoholism. The patient was unconscious, but showed signs of meningeal irritation. He was first treated with sulfadiazine, but remained in a comatose state for ten days. Then a trephination of the skull was performed and a positive culture of hemolytic *Staph. aureus* was isolated from the cerebrospinal fluid. Penicillin was then added to the treatment by intramuscular injection, and 25,000 units were instilled into each lateral ventricle by ventricular taps daily for four days. In spite of the combined therapy, the patient continued to run a febrile course with positive cerebrospinal fluid cultures. His course continued stormy with elevated temperature and pulse rate. The staphylococcus was found to be resistant to penicillin but susceptible to bacitracin. Therefore all other treatments were stopped and bacitracin was given by an intraventricular injection of 5,000 units dissolved in 4 c.c. of cerebrospinal fluid and 1 c.c. of distilled water, supplemented by 25,000 units intramuscularly every four hours. The administration of bacitracin was followed by a moderate rise of body temperature, ranging from 101° to 102° F. and lasting for five days. However, after the start of bacitracin therapy, repeated cerebrospinal fluid cultures were negative. Five days after the initiation of bacitracin, the patient slowly recovered consciousness. He first showed a response to painful stimuli and then began taking food by mouth. During the course of treatment he received a daily intraventricular injection of 5,000 units of bacitracin for six days and intramuscular injection of 25,000 units every four hours for eight days. Eight days after the cessation of bacitracin therapy there was no evidence of meningeal infection, and the patient's lowered mental status, the result of the infection and the cerebral contusion, thereafter slowly but steadily improved.

This case illustrates the development of a *Staph. aureus* meningitis following a compound fracture of the skull, in spite of eleven days of prophylactic treatment with sulfadiazine. Penicillin was then called upon to supplement the treatment. It was given in large doses, both by intramuscular and intraventricular routes, but it could neither change the clinical course nor sterilize the cerebrospinal fluid, for the organism was resistant to penicillin. However, a test of sensitivity to bacitracin showed the organism to be susceptible to that antibiotic. The infection promptly came under control when bacitracin was employed by the intramuscular and intraventricular routes. The latter pro-

cedure rapidly cleared the cerebrospinal fluid, as indicated by repeated negative cultures. The immediate rise of body temperature following the intraventricular administration might be interpreted as a reaction to the bacitracin, but the febrile reaction was in no way detrimental. In this case, it seems obvious that bacitracin saved the patient's life.

CASE 2.—F. B. (Bacitracin Study No. 1107), 56 years of age, was admitted to the Montreal Neurological Institute on Dec. 20, 1948, and was discharged March 5, 1949. Four days after the patient was admitted to the hospital a right-sided craniotomy was done for tumor. Seven days later, the wound showed evidence of infection with swelling, tenderness, and draining exudate. The neck became rigid and the temperature rose to 103° F. The cerebrospinal fluid showed 1,500 white blood cells. The bone flap was then removed. On this day the patient was given systemic penicillin and triple sulfonamides. These were continued for nineteen days without obvious effect. Five days later streptomycin was started and continued for fifteen days. In addition to the systemic treatment, the sulfonamides, streptomycin, and penicillin were instilled locally in the wound under the scalp. However, this combined treatment did not reach the subdural space. On the twenty-seventh day the patient's neck became increasingly rigid. There was a positive Kernig's sign and evidence of increased intracranial pressure. The wound was explored and a subdural abscess was found and drained. Cultures of the contents of the abscess and of the lumbar cerebrospinal fluid yielded a coagulase-positive staphylococcus which was resistant to 100 units of penicillin and required 32 units of streptomycin for inhibition, but it was sensitive to 0.85 unit of bacitracin. Bacitracin was therefore administered by local instillation into the abscess cavity in a dosage of 10,000 units in 10 c.c. of normal saline solution three times a day. This was reduced to 5,000 units after the eighth day and was continued for sixteen days. It was also given by the intrathecal route, 5,000 units in 5 c.c. of normal saline solution, on the first, second, fourth, and seventh days. Ten thousand units were injected intramuscularly every six hours for ten days. The temperature dropped to 99° F. on the fourth day of bacitracin therapy. The cerebrospinal fluid became clearer day by day and cultures promptly became negative. The patient thereafter made an uneventful recovery.

This illustrates the effectiveness of bacitracin in the treatment of staphylococcic meningitis when other therapy had failed. The antibiotic sensitivity test of the causal organism in this case, a coagulase-positive staphylococcus, indicated clearly that penicillin and streptomycin could not be expected to control this infection. However, bacitracin not only cured the meningitis, but together with the surgical drainage, cleared up the subdural abscess. Bacitracin was unquestionably lifesaving in this case.

CASE 3.—S. T. (Bacitracin Study No. 1100), 62 years of age, was admitted to the Lenox Hill Hospital, New York, on Sept. 10, 1948, and was discharged on Feb. 17, 1949. This patient received a cortical ablation of the right frontal lobe through an osteoplastic craniotomy for a schizophrenic psychosis. Postoperatively she was given prophylactic penicillin, 50,000 units every three hours for eight days, and then Duracillin, 300,000 units daily for seven days. Two days after the prophylactic therapy had been stopped, the patient became drowsy and fluctuation was noted beneath the scalp wound. Systemic penicillin was again administered in a dosage of 150,000 units every three hours. At the same time the wound was explored and a large quantity of purulent fluid was evacuated. Culture of the fluid showed *Staph. albus* which completely resisted penicillin but was sensitive to bacitracin. Bacitracin was then instilled into the wound every three hours through a sterile catheter, using 10,000 units in 10 c.c. of normal saline solution. Intramuscular

injections of 10,000 units of bacitracin were given every six hours for ten days. Six days later a portion of the bone flap was rongeured away and a subdural abscess was disclosed. Culture of the contents of this abscess also revealed the *Staph. albus*. Ten days after the beginning of bacitracin therapy, the wound culture became negative and remained so. The local instillation of bacitracin was carried on for thirty-two days and then the dose was halved and given twice a day. The patient made steady improvement and was ambulatory three weeks after the start of bacitracin therapy. The exudate diminished steadily and the cavity became obliterated until the wound was all healed except for a small sinus at the drainage site. The depths of the sinus were explored and a small bit of slough was removed. The wound then healed progressively.

This case illustrates a staphylococcic meningitis of localized type which formed a subdural abscess after cortical ablation. This condition might have been amenable to surgical treatment alone if the abscess had been well walled off, and if the cerebrospinal fluid had not become contaminated. The causative staphylococcus in this case was completely resistant to penicillin but susceptible to bacitracin. This adequately explains the fact that penicillin as a postoperative prophylactic measure for fifteen days failed to prevent the wound from becoming infected and a subdural abscess and meningitis from developing. There is no doubt in this case that the combined procedures of bacitracin therapy and surgical intervention controlled the infection after penicillin had failed.

CASE 4.—M. B. (Bacitracin Study No. 1080), a 6-week-old infant, was admitted to the Babies Hospital, New York, on Jan. 15, 1949, and was discharged on Feb. 13, 1949. This 6-week-old premature baby developed a huge abscess on the right side of the face, evidently arising from a pansinusitis. She had first been admitted to the Englewood Hospital in New Jersey for six days, and had been treated with systemic penicillin. Nasal and throat cultures revealed a *Staph. aureus* which was only slightly sensitive to penicillin. For this reason streptomycin was given, but the patient's condition did not improve. She was then transferred to Babies Hospital (New York). On admission her body temperature was subnormal. There was swelling all over the right side of her face, particularly around the eye, the cheek, and the ear. There was a purulent exudate from the right nostril and the right external auditory canal. The abscess was treated by aspiration and the instillation of penicillin. The baby was also given penicillin and streptomycin systemically. A lumbar puncture was performed and the spinal fluid was found to be turbid with 7,300 white blood cells with a differential of 85 per cent neutrocytes. Penicillin, 1,500 units, was therefore injected intrathecally. Cultures from the abscess of the face, from the nose, and from the blood revealed a coagulase-positive hemolytic *Staph. aureus*, but the cerebrospinal fluid unexpectedly showed no growth. On the next day the spinal canal was again tapped and cocci were seen in the smear of the cloudy fluid and *Staph. aureus* was obtained by culture. The systemic doses of penicillin were raised to 200,000 units every three hours and sodium sulfadiazine was started 0.06 Gm. every six hours. The body temperature ranged from normal to 102.4° F. On the third day the baby was lethargic. On the fourth day aureomycin was started by mouth and streptomycin by intrathecal therapy. Despite this treatment the blood and the cerebrospinal fluid cultures remained positive on the fourth, fifth, and sixth days. By this time a chest x-ray study revealed shadows which indicated pulmonary metastatic abscesses or patchy areas of pneumonia with some pleural fluid. The abscesses on the side of the face slowly spread down to the angle of the jaw. A small incision was therefore made at the lower margin and plastic catheters were inserted for the local instillation of penicillin. A similar procedure was carried out for a large metastatic abscess in the middle of the back, and another abscess on the dorsum of the right foot was incised and drained. However, the child showed no improvement and gradually sank into a coma. The organism was then tested and found to be sensitive to bacitracin. On the seventh

day after admission to Babies Hospital that drug was started in a dosage of 400 units per kilogram of body weight every six hours by intramuscular injection, and 500 units in 3 c.c. of normal saline solution twice a day by the intrathecal route. Bacitracin in a concentration of 500 units per c.c. was also instilled into the abscesses on the face and back through the plastic catheters. Laboratory tests had demonstrated synergism of bacitracin and penicillin, so systemic penicillin was continued. Oral aureomycin was also continued, but it was soon given up because of vomiting, which ceased as soon as this antibiotic was discontinued. On the third day of bacitracin therapy the child came out of the coma and her condition thereafter steadily improved. On the fourth day of bacitracin treatment the cerebrospinal fluid and blood cultures were negative and from then on remained so. On the fifth day of this treatment, intrathecal therapy was reduced to once daily for four more days and was then discontinued. The intramuscular injection was reduced to 200 units per kg. of body weight and was stopped one week later. The baby was discharged on the nineteenth day with all abscesses healed and in good condition. There was no sign of recurrence in any of the areas of infection, and x-ray films of the lungs showed complete resolution of the areas which with the older type of treatment would have broken down as lung abscesses.

Studies of the urine and blood gave essentially no indication of nephrotoxicity from the bacitracin. The urine showed a 1 plus albumin on admission and 2 plus on the following day, but during bacitracin treatment it was negative except on two days, when it was only 1 plus. A few granular casts were found on four occasions during treatment, but not on other days. The nonprotein nitrogen was 30 mg. per cent before bacitracin treatment and rose to 38 mg. per cent, but it was down to 31 mg. per cent a week after cessation of treatment.

This case illustrates staphylococcic meningitis probably of hematogenous origin, although the spread may have come from the nasal sinuses. Meningitis of this type, together with staphylococcic septicemia, is usually fatal, especially in undernourished and underweight infants or children. Although this baby had been treated by many agents, namely, penicillin, streptomycin, sulfadiazine, and aureomycin, there was no appreciable improvement in her condition until bacitracin therapy began. Intrathecal bacitracin undoubtedly cleared the staphylococcic meningitis, and the combined therapy of penicillin and bacitracin cured the staphylococcic septicemia as well as the pulmonary lesions. Aureomycin was of doubtful benefit in this case. Follow-up visits have shown a normal healthy child.

CASE 5.—F. M. (Bacitracin Study No. 1129), 27 years of age, was admitted to the University of Virginia Hospital on Aug. 17, 1949, and was discharged on Sept. 16, 1949. Four weeks prior to admission to the hospital this patient had several boils on the legs. One of these developed into a carbuncle which the doctor elected to incise, supplementing surgery with penicillin and sulfadiazine for a period of two days. Following this he began to have chills, fever, nausea, and vomiting. Some five days before admission to the hospital he was annoyed by headache and stiffness of his neck. He was then taken to a neighboring hospital where a lumbar puncture showed cloudy fluid with about 32,000 white blood cells, mostly polymorphonuclears. Culture of the spinal fluid at that time revealed a hemolytic *Staph. aureus*. He was started on sulfadiazine, 1 Gm. every four hours, and penicillin, 100,000 units every three hours, with a fall in the temperature, but progression of the meningeal signs. Penicillin was later increased to 200,000 units every two hours the day before he was transferred to the University of Virginia Hospital in Charlottesville, Va.

At the time of admission he was conscious, but his intellect was definitely impaired and he was having visual and auditory hallucinations. Temperature was 100.6° F. and in

general he appeared to be very severely and acutely ill. The pupils were constricted and the fundi showed bilateral marked choking of about 3 diopters. Examination of the heart and lungs was not remarkable except for a soft apical systolic murmur. The abdomen was tight without involuntary spasm. There was definite tenderness in the right flank on palpation. This tenderness later shifted and never presented any consistent localization. The neurological examination showed an extremely stiff neck with a positive Brudzinski and bilaterally positive Kernig's sign. Motor function was good and equal bilaterally. There were no definite localizing reflex changes and no other pathologic reflexes.

The white blood count on admission was 12,600, with about 3.5 million red blood cells and 13.5 Gm. of hemoglobin. Urine showed no abnormalities. Blood urea, chlorides, and carbon dioxide were within normal limits. A lumbar puncture was attempted shortly after admission to the hospital, but only a few drops of a thick, purulent material could be obtained. This was cultured, but there was no growth. The previous amounts of penicillin and sulfadiazine were continued. The following morning the patient seemed much more toxic and it was believed that his condition was rapidly becoming terminal. A neurosurgical consultation was obtained and it was advised, in view of the papilledema and other signs of increased intracranial pressure together with the obvious block in the ventricular system, that ventriculography was indicated. Therefore, on the third day, ventricular needles were inserted after cauterizing the dura and underlying cortex. Blood-tinged fluid, which was withdrawn in the amount of 45 c.c., was replaced by air. X-ray examination revealed no evidence of ventricular pressure. At this time 25,000 units of penicillin were instilled into the left lateral ventricle.

On the following day the patient was considerably worse, being in a stuporous condition and unable to respond. Because of the downward course following treatment with penicillin, it was decided to shift to the use of bacitracin. Ventricular needles were again inserted and at the same time a spinal puncture was performed. This time some very thick greenish material was aspirated from the lumbar site, and following this there was a free flow of turbid spinal fluid under a pressure of about 150 mm. of water. Culture of the thick pus which had been aspirated showed the hemolytic *Staph. aureus*. Unfortunately no tests were made of susceptibility to penicillin or bacitracin. Bacitracin, 9,800 units in 6 c.c. of saline solution and spinal fluid, was injected into the left lateral ventricle and the same amount into the lumbar intrathecal space. The day after this procedure the patient was considerably improved, his state of consciousness being approximately comparable to that at the time of admission. The intrathecal injection of bacitracin in the amount of 9,800 units was repeated and the same amount instilled into the right ventricle without obvious complications, except that the intrathecal injection of bacitracin seemed to be painful locally. During this time the patient remained febrile and toxic, but cultures from both the ventricular and spinal punctures were negative. A third instillation of bacitracin was made the next day intrathecally and intraventricularly on the right side in the same dosage as previously used. Cultures were again negative.

Following these procedures the patient made steady improvement. His mental perception rapidly returned to normal. There was no residual paralysis or paresis. The papilledema gradually receded. There was no albuminuria during bacitracin treatment. The blood urea fell from 26 mg. per cent to 18 mg. per cent and there was no change in the phenolsulfonphthalein excretion. From the fourth day following the initiation of bacitracin treatment the patient was completely afebrile. On that day the spinal fluid inhibited the growth of the organism in vitro in a dilution of 1 to 27. Just before discharge from the hospital the spinal fluid was found to be clear and colorless, with only twenty-four cells, all but one of which were lymphocytes. The chlorides were 720, protein 65, and sugar 41 mg. per cent.

This case is a clear-cut example of staphylococcus meningitis of hematogenous origin, of the type which before the days of chemotherapy was invariably fatal. It failed to respond to large doses of penicillin and sulfadiazine. When

a spinal block was discovered, intraventricular puncture revealed purulent cerebrospinal fluid, but the intraventricular injection of penicillin had no effect. With the patient rapidly failing and when the outlook seemed entirely hopeless, bacitracin was given intrathecally and intraventricularly with a dramatic response. After the first injection, cultures in both areas became negative and after only three instillations of bacitracin, the patient went on to a rapid and complete recovery without any evidence of toxicity or other untoward effect.

COMMENT

Delay in the treatment of any form of meningitis may have serious and even fatal consequences. It is the responsibility of the attending physician not only to make the diagnosis as soon as possible, but also to determine the causative organism and its susceptibility to the available antibacterial agents. When the diagnosis of meningitis is suspected, a diagnostic lumbar puncture should be performed immediately. If the puncture yields a cloudy fluid, a stained smear should be studied for bacterial forms. If cocci are found, an intrathecal injection of 10,000 units of penicillin or 5,000 to 10,000 units of bacitracin in 5 c.c. of saline solution is advocated. This will induce and maintain an antibiotic concentration in the cerebrospinal fluid for at least twelve hours. The initial treatment should then be repeated. In eighteen to twenty-four hours the infecting agent should be known and its susceptibility roughly determined. If the causative organism is sensitive to penicillin, further treatment with penicillin is indicated. However, if the organism is penicillin-resistant but bacitracin-sensitive, bacitracin is the drug of choice. It is also advisable to test the synergistic action of penicillin and bacitracin against the organism.[49] If there is any synergism, both antibiotics should be used together. The injection should be slow and by repeated barbotage, so that an even and higher concentration in the upper reaches of the cerebrospinal space may be obtained. If the patient does not show some improvement clinically within twenty-four to forty-eight hours, or if there are signs of blockage or obstruction of the spinal subarachnoid space, the injection should be given by the intracisternal route. If the patient still does not show any signs of improvement, ventricular puncture is indicated. If the puncture reveals cloudy fluid, the intraventricular instillation of penicillin or bacitracin or of both antibiotics should be given once or twice a day in a dosage of 5,000 to 10,000 units. Although these agents do not reach the cerebrospinal fluid in high concentration following intramuscular injections, supplementary treatment with 300,000 units of penicillin or 10,000 to 20,000 units of bacitracin should be given every eight hours by that route.

SUMMARY

The history of the treatment of staphylococcic meningitis has been reviewed. The results were generally bad until the advent of bacteriophage, the later sulfonamides, and the antibiotics. Since then treatment has been increasingly successful.

During the last two years, through centers set up to appraise the limitations of and the indications for the use of bacitracin, five patients with staphylococcal meningitis have been treated with this antibiotic. All of these patients had been treated unsuccessfully with other chemotherapeutic and antibiotic agents. Bacitracin, called upon after other measures had failed, clearly demonstrated its effectiveness in the treatment of this disease in every one of these patients. All recovered completely. It was the expressed opinion of those who saw these patients that there was no question about the prompt response to bacitracin treatment. While this series of cases is small in number, the fact that all of the patients responded suggests that bacitracin should be considered for the primary treatment of this disease. It may be stated that the causative organism is usually susceptible to bacitracin. Furthermore, the experimental and clinical data have shown that the intracranial, intraventricular, and intrathecal injection of bacitracin is far less toxic than are the other antibiotics and chemotherapeutic agents which have been tried.

REFERENCES

1. Neal, J. B.: Meningitis: Distribution According to Age and Etiology, J. A. M. A. **82**: 1429-1430, 1924.
2. Griffith, J. P. C., and Mitchell, A. G.: Diseases of Infants and Children, Vol. II, ed. 2, Philadelphia, 1927, W. B. Saunders Company, p. 315.
3. Porter, L., and Carter, W.: Management of the Sick Infant, ed. 3, St. Louis, 1927, The C. V. Mosby Company, p. 315.
4. Neal, J. B.: Purulent Meningitis Not Caused by the Meningococcus, in Tice's Practice of Medicine, Vol. X, Hagerstown, Md., 1921, W. F. Prior Co., p. 255.
5. Grinker, J.: In Forchheimer's Therapeusis of Internal Diseases, Vol. IV, New York, 1916, D. Appleton & Co.
6. Ballenger, H. C.: Meningitis (Staphylococcus Aureus) Secondary to Frontal Sinusitis; Operation and Recovery, J. A. M. A. **94**: 1040-1043, 1930.
7. Schless, R. A.: Staphylococcus Aureus Meningitis; Treatment With Specific Bacteriophage, Am. J. Dis. Child. **44**: 813-822, 1932.
8. MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Staphylococcic Meningitis From Hippocrates to LeGendre and Beaussenat; A Mortal Disease, Arch. Otolaryng. **37**: 199-208, 1943.
9. MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Recoveries From Staphylococcic Meningitis Following Bacteriophage Therapy, Arch. Otolaryng. **37**. 507-525, 1943.
10. Day, E. W.: Indications for and Results of Operative Treatment of Otitic Meningitis, Surg., Gynec. & Obst. **16**: 369-378, 1913.
11. Dandy, W. E.: The Treatment of Staphylococcus and Streptococcus Meningitis by Continuous Drainage of the Cisterna Magna, Surg., Gynec. & Obst. **39**: 761-774, 1924.
12. Moise, T. S.: Staphylococcus Meningitis Secondary to a Congenital Sacral Sinus, Surg., Gynec. & Obst. **42**: 394-397, 1926.
13. Earle, Sir James: The Chirurgical Work of Percivall Pott, Philadelphia, 1819, Vol. I, Webster, pp. 49-51.
14. Editorial: Epidemic Cerebro-Spinal Meningitis, Lancet **1**: 1010, 1905.
15. Gross, S. W.: An Examination of Causes, Diagnosis, and Operative Treatment of Compression of the Brain as Met With in Army Practice, Am. J. M. Sc. **66**: 57-63, 1873.
16. Galippe, V.: Du role des parasites infectieux dans la genese des accidents de l'évaluation de la dent de sagesse, J. d. conn. méd. prat. **9**: 314-316, 321-324, 1889.
17. Horsley, V.: Surgery of the Nervous System, Brit. M. J. **2**: 1286-1292, 1890.
18. Haynes, I. S.: The Surgical Treatment of Meningitis—Its Scope and Accomplishment, Tr. 18th Ann. Meet. Am. Laryngol., Rhinol. & Otol. Soc., 186-237, 1912.
19. Day, E. W.: Report of Eight Cases of Purulent Meningitis Operated Upon by the Haynes Method; Postmortem Findings, Laryngoscope **23**: 1041-1049, 1913.
20. Dench, E. B.: A Report of Three Cases of Otitic Meningitis Treated by Drainage of the Cisterna Magna, Tr. Am. Otol. Soc. **13**: 180-189, 1913.
21. MacNeal, W. J., Frisbee, F. C., and Blevins, A.: Reported Recoveries From Staphylococcic Meningitis, 1893-1941, Arch. Otolaryng. **37**: 349-370, 1943.

22. Seager, H. W.: The Epidemic of Cerebrospinal Meningitis at Lisbon, Lancet 2: 1188-1190, 1902.
23. Wolff, G.: Der Versuch einer neuen Meningitisbehandlung mit Silberpräparaten, Deutsche med. Wchnschr. 41: 1486-1489, 1915.
24. Watson-Williams, P.: Case of Labyrinthitis; Diffuse Purulent Meningitis; Labyrinthotomy; Recovery With Intra-venous and Intra-thecal Injections of Colloid Silver, J. Laryngol., Rhinol. & Otol. 35: 197-199, 1920.
25. Rocaz, P.: Méningite à staphylocoques traitée avec succès par les injections intrarachidinnes d'étain colloïdal, Gaz. hebd. d. sc. méd. de Bordeaux 41: 218-219, 1920.
26. Lamb, F. H.: Report of a Case of Staphylococcus Meningitis Treated With Intraventricular Injection of Gentian Violet, Arch. Pediat. 45: 306-309, 1928.
27. Lortat-Jacob, L., and Grivot, M.: Deux cas de méningites généralisées à staphylocoques. Utilité des vaccinations staphylococciques associées à la trépanation et aux rachicentèses, Bull. et mém. Soc. méd. d. hôp. de Par. 44: 1555-1559, 1920.
28. Dunlop, J. E.: Staphylococcic Meningitis With Recovery, J. A. M. A. 104: 1594-1595, 1935.
29. Frank, D. E.: Staphylococcic Meningitis With Autogenous Bacteriophage, J. M. Soc. New Jersey 33: 466-471, 1936.
30. Pilcher, C.: The Chemotherapy of Intracranial Infection, Ann. Surg. 119: 509-517, 1944.
31. McDermott, W., and Nelson, R. A.: The Transfer of Penicillin Into the Cerebrospinal Fluid Following Parenteral Administration, Am. J. Syph., Gonor. & Ven. Dis. 29: 403-415, 1945.
32. Dumoff-Stanley, E., Dowling, H. F., and Sweet, L. K.: The Absorption Into and the Distribution of Penicillin in Cerebrospinal Fluid, J. Clin. Investigation 25: 87-93, 1946.
33. Kinsman, J. M., and D'Alonzo, C. A.: Penetration of Penicillin Through Inflamed Meninges, New England J. Med. 234: 459-463, 1946.
34. Schwemlein, G. X., Barton, R. L., Bauer, T. J., Loewe, L., Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. 130: 340-341, 1946.
35. Walker, A. E., and Johnson, H. C.: Principles and Practice of Penicillin Therapy in Diseases of the Nervous System, Ann. Surg. 122: 1125-1135, 1945.
36. Siegal, S.: Transverse Myelopathy Following Recovery From Pneumococcic Meningitis, J. A. M. A. 129: 547-550, 1945.
37. Erickson, T. C., Masten, M. G., and Suckle, H. M.: Intrathecal Use of Penicillin, J. A. M. A. 132: 561-565, 1946.
38. Johnson, H. C., Walker, A. E., Case, T. J., and Kollros, J. J.: Effect of Antibiotic Substances on the Central Nervous System, Arch. Neurol. & Psychiat. 56: 184-197, 1946.
39. Neymann, C. A., Heilbrunn, G., and Youmans, G. P.: Experiments in the Treatment of Dementia Paralytica With Penicillin, J. A. M. A. 128: 433-434, 1945.
40. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin. A Note of Warning, J. A. M. A. 127: 217-219, 1945.
41. Johnson, B. A., Anker, H., and Meleney, F. L.: Bacitracin; A New Antibiotic Produced by a Member of the B. Subtilis Group, Science 102: 376-377, 1945.
42. Scudi, J. V., Coret, I. A., and Antopol, W.: Some Pharmacological Characteristics of Bacitracin. III. Chronic Toxicity Studies of Commercial Bacitracin in the Dog and Monkey, Proc. Soc. Exper. Biol. & Med. 66: 558-561, 1947.
43. Teng, P., and Meleney, F. L.: Bacitracin Levels in the Cerebrospinal Fluid After Parenteral Injections; Bacitracin Therapy of Experimental Staphylococcal Meningitis in the Dog, SURGERY 27: 403-413, 1950.
44. Teng, P.: Unpublished data.
45. Cone, W.: Personal communication.
46. Walker, A. E., Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions. The Convulsive Effects of Penicillin Applied to the Cortex of Monkey and Man, Surg., Gynec. & Obst. 81: 692-701, 1945.
47. Meleney, F. L., Longacre, A. B., Altemeier, W. A., Reisner, E. H., Jr., Pulaski, E. J., and Zintel, H. A.: The Efficacy and the Safety of the Systemic Administration of Bacitracin in Various Types of Surgical and Certain Medical Infections With an Analysis of 270 Cases, Surg., Gynec. & Obst. 89: 657-683, 1949.
48. Meleney, F. L., and Johnson, B. A.: Bacitracin Therapy. The First Hundred Cases of Surgical Infections Treated Locally With the Antibiotic, J. A. M. A. 133: 675-680, 1947.
49. Johnson, B. A.: Data to be published.
50. Roberts, W.: Mixed Influenza Bacillus—Staphylococcus Meningitis Cured With Sulfonamide Therapy, North Carolina M. J. 2: 494-495, 1941.
51. Hoyne, A. L.: Advances in the Treatment of Meningitis, J. Pediat. 19: 778-788, 1941.

52. Peters, R. H., Spector, S. S., Porter, E. L., and Pleasants, H., Jr.: Staphylococcus Aureus Meningitis, Pennsylvania M. J. **45**: 715-718, 1942.
53. McCune, W. S.: Staphylococcic Meningitis: Case Treated With Sulfadiazine With Recovery, J. Michigan M. Soc. **41**: 487-489, 1942.
54. Huber, I., and Nouvail, M. P.: Méningite à staphylocoques dorés guérie par le sulfathiazole non méthyle on 2090 P.P., Bull. et mém. Soc. méd. d. hôp. de Paris **58**: 142-143, 1942.
55. Aversa, T.: Sepsi stafilococcica (tromboflebite del seno cavernose, meningite purulenta ed osteomielite) guarita con trattamento sulfanudico, La Pediatria **51**: 164-171, 1943.
56. Tolan, J. F.: Staphylococcic Meningitis Treated With Sulfathiazole, Ann. Otol., Rhin. & Laryng. **52**: 207-214, 1943.
57. Brash, D.: Recovery in One Case of Staphylococcal Meningitis Treated by Chemotherapy, Glasgow M. J. **142**: 107-110, 1944.
58. Evans, A. L.: The Treatment of Intracranial Infections With Penicillin, J. A. M. A. **124**: 641-643, 1944.
59. McCune, W. S., and Evans, J. M.: Intraventricular Penicillin in the Treatment of Staphylococcal Meningitis, J. A. M. A. **125**: 705-706, 1944.
60. McCollum, W. D.. Cure of Staphylococcic Meningitis of Otitic Origin With Penicillin, Arch. Otolaryng. **40**: 514-515, 1944.
61. Worth, L. H.: Staphylococcal Leptomeningitis Treated With Intracisternal Penicillin, Lancet **249**: 634-635, 1945.
62. Gaumond, E., and Grandbois, J.: Plaie du front; méningite et septicémie à staphylocoque consecutive (traitement et guérison par la pénicilline), Laval méd. **10**: 101-109, 1945.
63. Amyot, R.: Méningite à staphylocoque traitée et guérie par la pénicilline, Union méd. du Canada **74**: 909-912, 1945.
64. Clemens, H. H.: Staphylococcus Albus Hemolyticus Meningitis in an Infant; Treatment With Sulfonamides Orally With Recovery, J. Pediat. **27**: 267-272, 1945.
65. Naffziger, H. C., Warmer, H., Stern, W. E., Fenlon, R., and McCorkle, H. J.: Penicillin in Central Nervous System and Skull Infections, J. A. M. A. **131**: 1183-1185, 1946.
66. Hjertaas, A. A.: Kraniefraktur komplisert med intrakranielt pneumatocele og meningitt behankelt med penicillin, Nord. Med. **29**: 467-468, 1946.
67. Wyke, B. D., and Vanderfield, G. K.: Repeated Intraventricular Injection of Penicillin in Severe Intracranial Infection. Purulent Meningitis and Ventriculitis so Treated, With Clinical Cure, M. J. Australia **2**: 523-525, 1946.
68. Hall, W. H., Alden, J., Burt, G. M., and Spink, W. W.: The Treatment of Pneumococcic and Staphylococcic Meningitis With Penicillin and Sulfonamides; Report of Twenty Cases, Minnesota Med. **29**: 553-559, 1946.
69. Miller, D., and Delohery, H. J.: Staphylococcal Meningitis and Ventriculitis: Cured by Penicillin, M. J. Australia **1**: 512-513, 1946.
70. Hoyne, A. L., and Brown, R. H.: Staphylococcic Meningitis: Its Rarity in the Newborn, Arch. Pediat. **65**: 175-182, 1948.

A METHOD OF PRODUCING EXPERIMENTAL INFECTED LONG BONE FRACTURES AND THEIR TREATMENT WITH PENICILLIN AND BONE GRAFTING

ALLEN H. JOHNSON, M.D., J. MALCOLM EDMISTON, M.D., H. J. MCCORKLE, M.D., AND HELEN WARMER, A.B., SAN FRANCISCO, CALIF.

(From the Department of Experimental Surgery, University of California Medical School)

A COMPLETE fracture of the tibia was produced in dogs under sodium pentobarbital anesthesia through a surgical incision in the lateral aspect of the leg. Infection was induced by crushing the muscle tissue exposed in the wound, contaminating the fracture site heavily with street dirt, and closing the incision. Within five to seven days all of these animals showed disruption of the wound with severe acute suppurative infection. After approximately thirty days, the infectious process usually subsided to form a chronic granulating draining sinus. X-ray studies of the bones revealed evidence of osteomyelitis with rarefaction, sequestration, and involucrum formation at the site of the infected fracture (Fig. 1). The bacteria cultured from the draining sinus tracts are listed in Table I.

Twelve animals with well-established infected fractures were selected for experiments to test the efficacy of penicillin therapy in conjunction with bone-grafting procedures. Six animals served as untreated controls. The remaining six animals received 100,000 units each of penicillin daily by intramuscular injection every four hours for five days preceding, and for twenty-one days following, operation for treatment of the infected fracture.

The operation on all animals consisted of complete excision of sinus tracts, infected granulations, scar tissue, sequestra, and infected bone, and repair of the fracture with a cancellous graft from the ilium or a sliding cortical bone graft held in position with fine stainless steel wire. The extremity was immobilized in a plaster of Paris cast. X-ray studies were done at monthly intervals. All surviving animals were sacrificed for gross and histologic study three months after the bone-grafting procedure.

Of the six animals receiving penicillin therapy, four showed improvement during the preoperative period. The sinus tracts closed in two animals, and in two the sinuses became smaller with less drainage. The other two animals showed no detectable change. Postoperatively the appetite, nutrition, and general condition of five of the penicillin-treated animals were good, and all six survived the three-month follow-up period. This condition contrasted sharply with the condition of the six untreated control animals in which malnutrition and sepsis, associated with the peculiar foul odor of suppurating bone, prevailed. Four of the six untreated control animals died before the end of the three-month period, and the two survivors were in extremely poor condition (Table II).

The soft tissue wounds healed *per primam* in four of the six penicillin-treated animals, and in two animals there was trivial infection with drainage

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California.

Received for publication, Nov. 21, 1949.

Fig. 1.—Reproduction of x-ray of dog's tibia four weeks after infected fracture was established.

Fig. 2.

Fig. 3.

Fig. 2.—Reproduction of x-ray of penicillin-treated animal three months after bone grafting showing incorporation of graft in healing fracture.

Fig. 3.—Reproduction of x-ray of untreated control animal showing sequestration of graft, bone destruction, and non-union.

TABLE I

ORGANISM	NUMBER OF ANIMALS	PENICILLIN SUSCEPTIBLE	PENICILLIN RESISTANT*
Clostridium	7	6	1
Nonhemolytic *Staphylococcus aureus*	5	4	1
Beta hemolytic streptococcus	4	3	1
Hemolytic *Staphylococcus albus*	4	2	2
Aerobic spore-forming bacilli	1	1	0
Anaerobic streptococcus	1	1	0
Bacterioid	1	1	0
Diphtheroid	3	0	3
Streptococcus faecalis	2	0	2
Escherichia coli	1	0	1
Proteus	1	0	1

*Organisms not susceptible to 1/10 Oxford unit per cubic centimeter.

TABLE II

	NUMBER OF ANIMALS	GENERAL POSTOPERATIVE CONDITION		
		GOOD	POOR	DIED
Penicillin treated	6	5	1	0
Untreated controls	6	0	2	4

from sinus tracts from which penicillin-resistant organisms were recovered. The wounds broke down with foul suppuration in all untreated control animals (Table III). Two of these wounds finally closed by granulation after the grafts were extruded.

TABLE III

	NUMBER OF ANIMALS	SOFT TISSUE WOUND HEALING		
		PER PRIMAM	TRIVIAL INFECTION	GROSS INFECTION
Penicillin treated	6	4	2	0
Untreated controls	6	0	0	6

All of the bone grafts remained viable in the animals treated with penicillin. Bony union occurred in four, fibrous union in one, and non-union in one animal (Fig. 2). The animals that failed to obtain bony union were the ones that had trivial infection with penicillin-resistant organisms. There was no bony union in any of the untreated control animals. The grafts were found as loose sequestra in pus in three control animals (Fig. 3). In two others the grafts were extruded, and in one untreated control animal fibrous union occurred (Table IV).

TABLE IV

	NUMBER OF ANIMALS	UNION OF GRAFT		
		BONY	FIBROUS	NONE
Penicillin treated	6	4	1	1
Untreated controls	6	0	1	5

SUMMARY

A method for producing experimental infected fractures is described. Superior healing of soft tissues, bone, and bone grafts was obtained in animals that received penicillin therapy in conjunction with adequate surgical removal of infected tissue and immobilization, as compared with the results in controls that received similar surgical management and immobilization, but were not given antibiotic therapy.

ESOPHAGEAL ANASTOMOSIS: TYPES AND METHODS OF SUTURE

R. W. Postlethwait, M.D.,* W. Ralph Deaton, Jr., M.D., H. H. Bradshaw, M.D., and R. W. Williams, M.D., Winston-Salem, N. C.

(From the Department of Surgery, Bowman-Gray School of Medicine of Wake Forest College)

PROGRESS in surgery of the esophagus has been rapid during the past few years but a number of problems remain which merit study. Anastomoses involving the esophagus are more hazardous than in most of the remainder of the gastrointestinal tract because of the absence of a serosal covering and the relatively smaller blood supply. Any factor, therefore, which might enhance healing should be considered. In this study, an attempt was made to evaluate the various types and methods of suture of the esophagus. The correction of esophageal atresia with or without tracheoesophageal fistula was not considered, as this problem is separate and distinct because of the small size and delicacy of the segments, especially the distal one.

Various types of sutures have been used in the experimental animal, and in the adult human being after resection for carcinoma or stricture. Miller and Andrus[1] used a modification of the Halsted bulkhead method for esophagogastric anastomosis in dogs, with an inner layer of interrupted silk mattress sutures and a continuous silk suture in the muscularis. Saint and Mann[2] resected up to 4 cm. of the esophagus in dogs and for the esophagoesophageal anastomosis employed two layers of silk in the same manner as Miller and Andrus. Adams, Escudero, Aronsohn, and Shaw[3] used a two-layer interrupted linen suture for esophagogastric anastomosis in dogs. In a few of the animals a two-layer continuous linen suture interrupted at four points was employed. Carter, Stevenson, and Abbott[4] used continuous or interrupted sutures for the inner layer in about an equal number of esophagogastric anastomoses in dogs. The continuous suture was interrupted at the halves or the quadrants by a silk suture. No striking difference was noted, but their clinical impression was that less interference with the blood supply occurred with the interrupted suture. Catgut or silk was used for the inner layer without noticeable difference in the operative results. For the outer layer of sutures, interrupted Lembert sutures of fine silk were used in all animals. Swenson and Clatworthy,[5] after resection of up to 80 per cent of the esophagus in dogs, performed a two-layer end-to-end esophageal anastomosis with interrupted 0000 silk. The inner layer was mucosal and the outer included the muscular coat with "some of the submucosa."

Clark and Adams[6] performed side-to-side esophagogastric anastomoses above benign strictures of the esophagus in patients, employing two layers of either interrupted or continuous linen sutures. Garlock[7] has repeatedly emphasized the importance of meticulous technique in anastomosis after resection for carcinoma. He used two layers of interrupted silk, the outer telescoping the stomach over the esophagus. Sweet[8] also emphasized the importance of careful

Presented at the Forum on Fundamental Surgical Problems, Clinical Congress of the American College of Surgeons, Chicago, October, 1949.

Received for publication, Nov. 22, 1949.

*Now at the Medical College of South Carolina, Charleston, S. C.

anastomosis, and in his esophagogastric anastomosis employed a three-layer interrupted silk technique. The first layer of mattress sutures approximated the muscularis of the esophagus to the seromuscularis of the stomach; the second, muscularis to muscularis; and the third, mucosa to mucosa. Nagel and Menke,[9] for esophagogastric anastomoses following resection for carcinoma, used an outer layer of interrupted silk mattress sutures and an inner layer of continuous 00 chromic catgut. Thorek,[10] in the same procedure, preferred an outer layer of interrupted mattress sutures of cotton and an inner layer of through-and-through interrupted cotton sutures.

In an effort to determine whether one type of suture had any advantages over another the following experiment was carried out.

METHODS

Mongrel dogs weighing 8 to 36 pounds were used; the majority weighed between 12 and 18 pounds. Thoracotomy on the left was performed under Nembutal anesthesia with endotracheal intubation and intermittent positive pressure. The lower one-third of the esophagus was freed up, with care to preserve the vagus nerves and as much of the blood supply as possible. The esophagus was divided transversely and immediately anastomosed end-to-end with two layers of sutures. The outer layer was through the muscularis and some of the submucosa, and the inner layer included the submucosa and mucosa with the knot tied within the lumen. Sutures were placed about 2 mm. from the cut edge and from 2 to 3 mm. apart. Forceps were employed as little as possible. No portion of the esophagus was removed so that tension was not a factor. No fixation sutures were used and the pleura was not closed over the site of anastomosis. Only esophagoesophageal anastomoses were studied in this series.

Six groups of dogs were studied, divided as follows: Group 1, interrupted silk sutures in both layers; Group 2, continuous silk in both layers; Group 3, interrupted catgut in both layers; Group 4, continuous catgut in both layers; Group 5, interrupted simple silk in the inner layer and interrupted silk mattress in the outer layer; and Group 6, continuous catgut in the inner layer and interrupted silk in the outer. The interrupted were all simple through-and-through sutures except for the mattress sutures. The continuous sutures were tied at one point and locked one-half of the way around the anastomosis. Five zero silk and five zero catgut sutures were used.

The dogs were allowed water for the first two days. Soft food was then given until the seventh or eighth day, when they received the regular kennel rations. No parenteral fluids or antibiotics were administered. With the few exceptions noted in the results, the esophagus was removed in six or ninety days for gross and microscopic study. These time intervals were selected because early healing should be fairly well advanced at six days and by ninety days stricture would probably have developed if this was to occur.

RESULTS

Group 1, Interrupted Silk.—Six dogs were sacrificed at six days and a seventh dog at nine days. Grossly, the esophagus of two dogs showed slight

mucosal separation and in the others healing appeared to be very satisfactory. Most of the sutures were still in place. Microscopically, a moderate number of round cells were seen except in the dogs which showed mucosal separation, and here acute inflammatory cells were present in the mucosa and immediate submucosa. A suture was identified in the sections from each of the six specimens. In one specimen the suture was well encapsulated, in three it was surrounded by round cells, and in two by acute inflammatory cells.

Six dogs were sacrificed at the end of ninety days. In two dogs one suture remained and in a third there were three sutures still in place. Healing was excellent in all instances and no stricture occurred. Microscopically, all showed mature narrow scars. Only one suture was found in this group microscopically and this was encapsulated, but immediately surrounding the suture were both acute and chronic inflammatory cells.

One dog, on whom interrupted silk sutures had been used for the anastomosis, died of pneumonia at the end of forty-two days. The anastomosis was well healed both grossly and microscopically and no stricture was present.

Group 2, Continuous Silk.—Three dogs were sacrificed at the end of six days. Two showed good early healing with all sutures in place. In the third the sutures had pulled out at one area to allow leaking with resultant pneumothorax and early empyema. In this dog, microscopically, the mucosa was ulcerated and the interval filled with fibrin and polymorphonuclear leucocytes. In the other dogs healing was well advanced and a moderate number of round cells were seen. In both the latter specimens a suture surrounded by acute inflammatory cells was seen microscopically.

Two dogs in this group were sacrificed at forty-two days. Both showed excellent healing grossly, and on microscopic study in one a narrow scar of mature connective tissue was present. In the other, connective tissue formation was also excellent but the scar was wider than usual. One encapsulated suture was seen.

Eight dogs having continuous silk sutures were sacrificed at ninety days. Grossly, no strictures were found and healing was excellent with the following exceptions. In five of the dogs a small area of granulation tissue was evident in the mucosa at one point of the anastomosis in each. A probe inserted into this led to the outer suture placed in the muscular layer. As far as could be determined no leakage had occurred. Microscopically, those sections which were taken through these granulating areas showed acute inflammatory reaction, but sections through the other areas showed mature scar tissue. Three sutures were seen which were well encapsulated and two were surrounded by polymorphonuclear leucocytes.

Group 3, Interrupted Catgut.—Two dogs were sacrificed at six days and both showed excellent healing both grossly and microscopically. In one section a suture was surrounded by round cells.

The specimen was obtained from three dogs in ninety days and no strictures occurred. All showed excellent healing both grossly and microscopically. Two sutures were seen surrounded by round cells.

Group 4, Continuous Catgut.—Two dogs were sacrificed in six days. In both the healing was well advanced grossly. Microscopic sections showed good early healing and a moderate number of chronic inflammatory cells.

The esophagus was removed from four dogs at the end of ninety days. Grossly, healing was excellent and in two it was difficult to recognize the site of

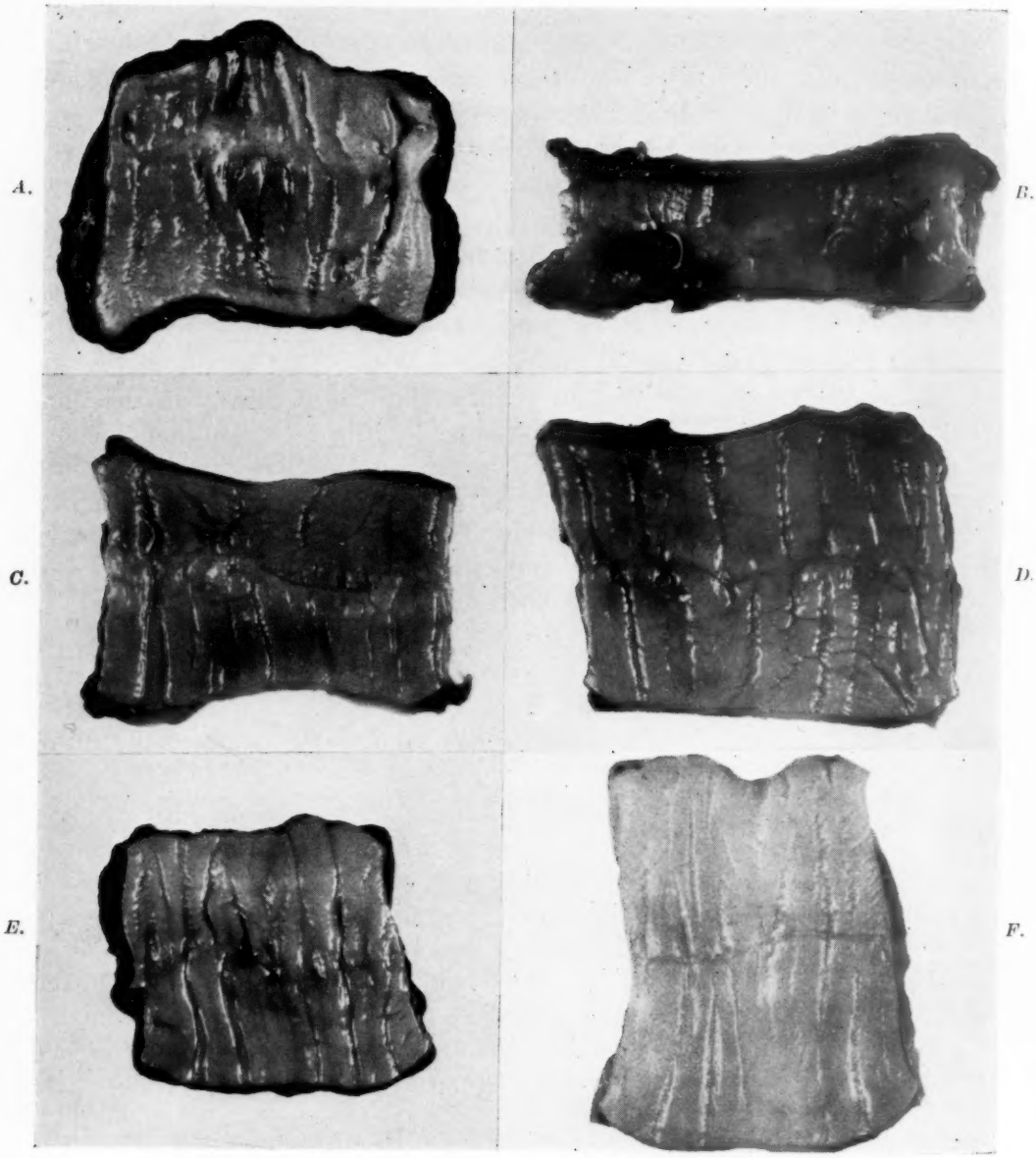


Fig. 1.—Esophageal anastomoses in dogs; specimens removed ninety days after operation. All had two layers. *A*, interrupted silk. *B*, continuous silk. Note two sinus openings, one leading to continuous muscle suture and the other with a portion of this suture protruding. *C*, interrupted five zero chromic catgut. *D*, continuous five zero chromic catgut. *E*, interrupted silk mattress sutures in muscle, simple interrupted silk in mucosa. *F*, interrupted simple silk sutures in muscle, continuous five zero chromic catgut in mucosa. Note absence of stricture in all specimens.

the anastomosis. No strictures were found. Microscopically, all showed mature scar tissue. Sutures surrounded by round cells were seen in three sections.

Two dogs who had continuous catgut suture died. The first expired forty-three days after operation and had a massive empyema on the left. Both grossly and microscopically, however, the anastomosis was well healed. The second dog, through an error, was subjected to craniotomy and died of pneumonia the second day after this procedure. This was the twenty-ninth day after esophageal anastomosis. The esophagus showed excellent healing both grossly and microscopically and one encapsulated suture was seen.

Group 5, Mattress Sutures for Outer Layer.—In a group of six dogs mattress sutures of silk were used in the muscular layer rather than the simple interrupted sutures. The mucosal sutures were interrupted silk.

Three dogs were sacrificed at the end of six days. Two showed good healing grossly and in the third the mucosa was separated. In the latter, microscopically, the submucosa was infiltrated by polymorphonuclear leucocytes and the mucosa ulcerated. The others showed good fibroblastic proliferation with a moderate number of chronic inflammatory cells. A suture within an abscess was seen in two sections.

Three dogs were sacrificed at the end of ninety days and both grossly and microscopically healing was excellent. No stricture was noted. In all three dogs, however, sections showed a portion of suture which was surrounded by acute inflammatory cells.

Group 6, Catgut and Silk.—In twelve dogs, the anastomosis was performed with an inner layer of continuous catgut and an outer layer of interrupted silk. The esophagus was removed from six dogs after six days. Healing appeared well advanced grossly and on microscopic study excellent early healing was found in all six. Sutures surrounded by acute and chronic inflammatory cells were noted in all but one section.

After ninety days, the remaining six dogs were again operated upon. Grossly, all appeared very well healed without signs of infection or stricture. Microscopic sections showed mature narrow scars.

DISCUSSION

In the entire group of fifty-nine dogs, the anastomosis of only one dog developed a leak at the suture line. This was with continuous silk suture. Another dog died of empyema after a continuous catgut anastomosis. Whether a separation of the suture line with leakage occurred or contamination at operation took place is conjectural, but the latter appeared more likely in view of the excellent healing. With continuous silk, points of granulation tissue in the mucosa were noted. Each led to the suture in the outer layer. These points of poor healing may have been due to placing the suture too closely beneath the mucosa, with subsequent infection and persistent drainage. The continuous suture may also have interfered with the blood supply to a greater extent than the interrupted, although areas of granulation tissue did not occur with the continuous catgut. Theoretically, one factor may have been the limited dilatation imposed at the anastomosis by the continuous suture which caused the latter

to cut through the mucosa at the time of swallowing. The catgut sutures in the histologic sections were usually fragmented and surrounded or infiltrated by round cells. Conversely, the silk sutures were usually surrounded by polymorphonuclear leucocytes.

No instance of stricture was encountered in the entire series, as determined by simple gross inspection of the specimen. Barium swallow and fluoroscopy were not employed. The animals did not regurgitate food, suggesting the absence of stricture. At the time of reoperation, a slight degree of esophageal dilatation above the anastomosis was infrequently encountered and this was never at all marked.

It is well known that a continuous suture may produce more strangulation of tissue than interrupted sutures. In these studies, with no tension on the suture line and maximum preservation of blood supply, a continuous suture for the mucosal layer produced healing as satisfactory as the interrupted sutures, with the exception of one animal with continuous silk. Little difference was noted between silk and catgut in the inner layer. For the muscular layer, interrupted silk or catgut showed equally good healing, whereas for a continuous suture, catgut appeared better than silk.

From this study, the only statement which can be made is that a meticuously performed end-to-end esophageal anastomosis in dogs will heal satisfactorily with either silk or catgut sutures. Interrupted sutures are somewhat preferable to the continuous, particularly in the muscular layer. Simple sutures serve as well as mattress in the muscular layer. From the over-all standpoint of technique and healing (if one preferred method must be selected on the basis of this experiment) a mucosal suture of continuous catgut and a muscular layer of interrupted silk would appear to be best.

CONCLUSION

A meticulous technique in performing esophageal anastomosis is more important than the type or method of suture employed. Preference, however, is given to an inner mucosal layer of continuous catgut and an outer muscular layer of interrupted silk.

REFERENCES

1. Miller, R. T., Jr., and Andrus, W. D. W.: Experimental Surgery of the Thoracic Esophagus, Bull. Johns Hopkins Hosp. **34:** 109-114, 1923.
2. Saint, J. H., and Mann, F. C.: Experimental Surgery of the Esophagus, Arch. Surg. **18:** 2324-2338, 1929.
3. Adams, W. E., Escudero, L., Aronsohn, H. G., and Shaw, M. M.: Resection of the Thoracic Esophagus, J. Thoracic Surg. **7:** 605-620, 1938.
4. Carter, B. N., Stevenson, J., and Abbott, O. A.: Experimental Esophagogastrostomy, J. Thoracic Surg. **10:** 446-470, 1941.
5. Swenson, O., and Clatworthy, H. W.: Partial Esophagectomy With End-to-End Anastomosis in the Posterior Mediastinum, SURGERY **25:** 839-848, 1949.
6. Clark, D. E., and Adams, W. E.: Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, Ann. Surg. **122:** 942-953, 1945.
7. Garlock, J. H.: Causes of Mortality Following Radical Resection of the Esophagus for Carcinoma, J. Thoracic Surg. **13:** 415-423, 1944.
8. Sweet, R. H.: Transthoracic Gastrectomy and Esophagectomy for Carcinoma of the Stomach and Esophagus, Clinics **3:** 1288-1315, 1945.
9. Nagel, G. W., and Menke, J. F.: Transthoracic Operations for Neoplasms of the Esophagus and Stomach, Surg., Gynec. & Obst. **83:** 657-666, 1946.
10. Thorek, P.: Surgical Treatment for Carcinoma of the Esophagus, Illinois M. J. **92:** 329-337, 1947.

MANAGEMENT OF PLEURAL TEARS DURING THORACOPLASTY

ELLIOTT MICHELSON, M.D.,* BALTIMORE, MD.

PLEURAL tears during thoracoplasty may or may not result in a major complication during the postoperative period, depending upon the pulmonary reserve of the patient. In good-risk patients with unilateral involvement, minimal pulmonary secretions, and good respiratory function, the addition of a traumatic pneumothorax is not hazardous. If the hemopneumothorax absorbs slowly, a fibrous peel may envelop the lung and its parieties with consequent impairment of respiratory function. In the poor-risk patient with marked secretions and low respiratory reserve, the additional reduction in function imposed by a hemopneumothorax may be serious and lead to severe anoxia and irreversible pulmonary edema. In the early postoperative period, complicating factors such as mediastinal shift and contralateral atelectasis may further embarrass respiration so that maximum respiratory function of the ipsilateral lung is urgently needed.

This paper concerns a method for closure of pleural tears which allows rapid expansion of the lung and early removal of air and fluid from the pleural space.

In the past year, while attempting a thoracoplasty over a pneumonic right upper lobe, a pleural tear resulted in dislocation of the upper lobe below the level of the hilum. In order to reduce the number of resected ribs necessary to collapse this lobe, a catheter was inserted into the pleural space, suction applied, and complete re-expansion of the lung followed, with the right upper lobe rising into the apical paravertebral gutter. No pleural effusion developed. Heartened by this result, all subsequent pleural tears have been treated by intrapleural catheter drainage instituted at the time of operation. The results have been uniformly excellent; the Pnx is absent at the end of the operation, the extrafascial fluid seeping into the pleural space is removed quickly, and no secondary pleural effusion follows.

The technique is simple, requires no special instruments, and can be performed in a few minutes. No attempt is made to close the pleural tear, although it may be plugged with a sponge temporarily. As soon as the opening is discovered, an aspirating needle is inserted through an exposed intercostal space approximately at the midaxillary line one or two interspaces below the lowest rib to be resected. If a pneumothorax space is found, a trocar cannula is in-

---

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Read at the Upstate (New York) Society of Thoracic Surgeons, Lake Placid, N. Y., May, 1949.

*Formerly Chief of Surgery, Veterans Hospital, Sunmount, N. Y.

serted, a small urethral catheter (French 14 or 16) is fed into the pleural cavity, and immediately connected with an underwater drainage bottle. After rib resection is completed, but prior to closure of muscle layers, a small incision is made in the skin and the catheter is extracted through this opening. A silk mattress suture is placed in the skin wound about the catheter and is tied later when the catheter is removed. The catheter is again attached to underwater drainage, and, when the patient is returned to the ward, continuous mild suction may be applied. We have placed 4 to 8 cm. of catheter within the pleural space and it appears to function as well as one with the tip inserted just beyond the parietal pleural wall. The lung expands, quickly closing the tear, and the pneumothorax is completely removed by the end of operation. Fluid in the subscapular space will continue to seep into the pleural space for approximately twenty-four hours and it is, therefore, desirable to continue suction drainage during this period.

The first case, already cited, had bilateral pulmonary tuberculosis and a pneumonic right upper lobe. The catheter was inserted the day after operation and removed two days later with no subsequent pleural effusion. There were four other pleural tears subsequently, and all were treated by intrapleural catheter drainage performed at the time of operation. The catheters were removed on the first day after operation and no pleural effusions developed later. Two of the cases are worthy of comment. One patient had a left seven-rib thoracoplasty on June 14, 1949, and on Dec. 5, 1949, during a right six-rib supraperiosteal pneumonolysis with Lucite plombage, under local anesthesia, the pleura was torn. Function studies* prior to operation revealed a maximum breathing capacity of 82 L. per minute, with the right lung performing 64 per cent of the total ventilation and 65 per cent of the total oxygen consumption. The pleural catheter was inserted before the patient noted any respiratory symptoms and no pneumothorax was present on x-ray examination at the end of operation. The patient had no subjective or objective evidence of diminished respiratory reserve during convalescence.

The other patient had bilateral cavitary disease and a right Monaldi drainage tube. The respiratory reserve was low, with but 48 L. per minute maximum breathing capacity, and a residual air of 53 per cent (of total lung volume) verified the presence of severe emphysema. Bronchospirometric studies showed that the left lung performed 61 per cent of the total ventilation and absorbed 71 per cent of the total oxygen. The pleura was torn during a left supraperiosteal pneumonolysis with Lucite plombage, performed on July 12, 1949, under local anesthesia. The patient experienced mild dyspnea until the catheter was inserted. The drainage tube was removed on the following day and convalescence was otherwise uneventful.

There have been no complications following the use of intrapleural catheter suction for pleural tears. The patient experiences no additional pain or discomfort. Roentgenograms taken immediately after operation have shown no trace of pneumothorax. The rapid expansion of the lung closes the pleural tear and allows the subscapular fluid to accentuate the collapse. Aspirations of the pleural space have not been necessary in any case, and in only one instance has there been enough fluid or reaction to produce obliteration of the costophrenic sulcus. The immediate drainage is bloody, but the total drainage is

*Respiratory function studies were performed by Dr. George Wright of Physiologic Laboratory, Trudeau Foundation, Saranac Lake, N. Y.

serohemorrhagic and has been less than 100 c.c. in all cases. This would suggest that the mechanism of large pleural effusions following a pleural tear is not due to the original small amount of hemorrhagic fluid seeping into the pleural cavity, but to the pleural exudation stimulated by the presence of blood.

CONCLUSIONS

Pleural tears during thoracoplasty may produce respiratory distress by the presence of pneumothorax and subsequent pleural effusion. The use of intrapleural catheter drainage instituted at the time of operation is suggested. By this procedure, the tear is closed by the expanding lung, the pneumothorax is obliterated and extrafascial fluid seeping into the pleural cavity is quickly removed. The method is especially recommended for those thoracoplasty patients with low respiratory reserve.

REFERENCE

1. Melick, D. W., and Spooner, M.: Experimental Hemithorax, J. Thoracic Surg. **14**: 461, 1945.

EFFECT OF VAGOTOMY ON INTESTINAL ACTIVITY

SALMON FAIK, M.D.,* JOHN H. GRINDLAY, M.D., AND FRANK C. MANN, M.D.,
ROCHESTER, MINN.

(From the Division of Experimental Medicine, Mayo Foundation and Mayo Clinic)

THE re-application of vagotomy as a therapeutic measure, especially in regard to the surgical treatment of peptic ulcer, has caused a renewal of studies on the functions of the vagi nerves in relation to the physiologic mechanisms of the gastrointestinal tract. Most of such studies have been concerned with the effect of vagotomy on gastric secretion and gastric motility.

The recent excellent review of the literature on vagotomy by Alvarez[1] clearly indicated that the most demonstrable effects of intrathoracic vagotomy have been exerted on gastric functions. However, the vagi contain nerve fibers which innervate other portions of the gastrointestinal tract and visceral organs, although to a more limited extent than the stomach, and information regarding the effects, if any, of vagotomy upon these extragastric structures must be obtained before a complete physiologic appraisal of the results of section of the vagi can be made. The context of the review by Alvarez suggested that further researches are desirable on the effect of intrathoracic vagotomy on organs other than the stomach, even though the results of such studies would probably be much less striking than those obtained concerning gastric functions.

Our investigation was undertaken as an attempt to determine if vagotomy affected some of the specific types of activity of the intestinal tract.

METHOD

Healthy, trained, female dogs were used in this investigation. The animals were trained to lie quietly on their side and to eat in this position on a comfortable padded table. Various loops of intestine were exteriorized according to the technique developed in this laboratory.[2, 3] All operative procedures, both in exteriorizing the intestine and in section of the vagi, were performed with the animals under the influence of ether anesthesia and with the use of sterile technique. Multiple exteriorized loops of intestine were made in each animal. Two animals had three loops exteriorized at various levels containing one segment each of duodenum, of jejunum, and of ileum. A loop of duodenum and a loop of jejunum were exteriorized in each of three dogs, and in one animal the exteriorized loops were of duodenum and ileum. Intestinal motility was recorded photographically by the method described by Mathur and two of us (Mann, Grindlay).[4]

Daily observations and records were made under conditions of fasting and also after feeding to the dogs a standard meal for a period of about three months before vagotomy. Through an intercostal incision the vagi were

---

Abridgment of thesis submitted by Dr. Faik to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science.

Received for publication, Oct. 19, 1949.

*Fellow in Experimental Surgery.

evulsed for their entire length between the diaphragm and the hilum of the lung. The results of numerous such operations in the dog have shown that all the vagal fibers are severed and that regeneration does not occur. After recovery of the animals from the vagotomy, recordings were made under conditions similar to those of the control period. Studies were made for six months and longer after vagotomy.

RESULTS

The general effects of intrathoracic vagotomy were exhibited by these animals. After vagotomy the dogs appeared to be quieter and less alert. They showed an increase in salivation and frequently vomited a ropy, mucous, gastric content. Diarrhea developed. The vomiting and diarrhea disappeared at the end of the third postoperative day in all of the animals except one. In this animal the diarrhea persisted until death occurred six weeks after operation. The animals lost interest in food and ate with reluctance, even after long periods of fasting. A decrease in appetite is not unusual in vagotomized dogs.

Intestinal motility differs to a certain extent among individual dogs. It also differs slightly in the same animal on different days and at different times of the day, particularly in relation to feeding time and after feeding. However, a composite picture of intestinal activity can be obtained by a careful study of the records.

As noted previously, the intestinal tract of normal dogs after a fast of twenty-four hours or more is quiescent, except for an occasional short period of activity which often consists of rhythmic contractions of small amplitude.[4, 5] In general, the pattern of activity is similar in each of the different segments of the intestine, but often the jejunum of the fasting animal exhibits the most activity, and the rate of rhythmic segmentation decreases progressively from pylorus to cecum, but is constant for any specific loop of intestine. After vagotomy the pattern of intestinal activity was not altered in the fasting state, but it always required a longer fasting period before the intestine became quiescent. Rhythmic segmentation was not affected in either rate or gradient phenomenon.

The sight and smell of food usually are followed by activity of the duodenum and activity to a lesser extent in the jejunum and ileum in normal dogs that have fasted for twenty-four hours or longer. This psychic reflex was readily produced in the animals used in this investigation before vagotomy, but was not recognized after evulsion of the vagi.

The ingestion of food after a period of fasting initiates a regular cycle of intestinal activity, the feeding reflex, in a normal animal. The activity begins in the duodenum immediately after a meal, and passes caudally as a wave to the terminal portion of the ileum. This rapid motor response to feeding is followed by prolonged activity which gradually diminishes until the entire intestine becomes almost quiescent.

The animals observed in this research had a normal feeding reaction followed by the normal pattern of intestinal activity noted during digestion. The

feeding reflex in these animals was not affected by vagotomy, as had been noted previously,[5] except for a slight delay in its appearance and a decrease in the duration of the initial burst of activity. The pattern of intestinal activity during digestion after vagotomy was altered from the normal as follows: there was a decrease in the waves of peristalsis, in both number and amplitude, and an increase in the occurrence of rhythmic segmentation; the tonus waves were

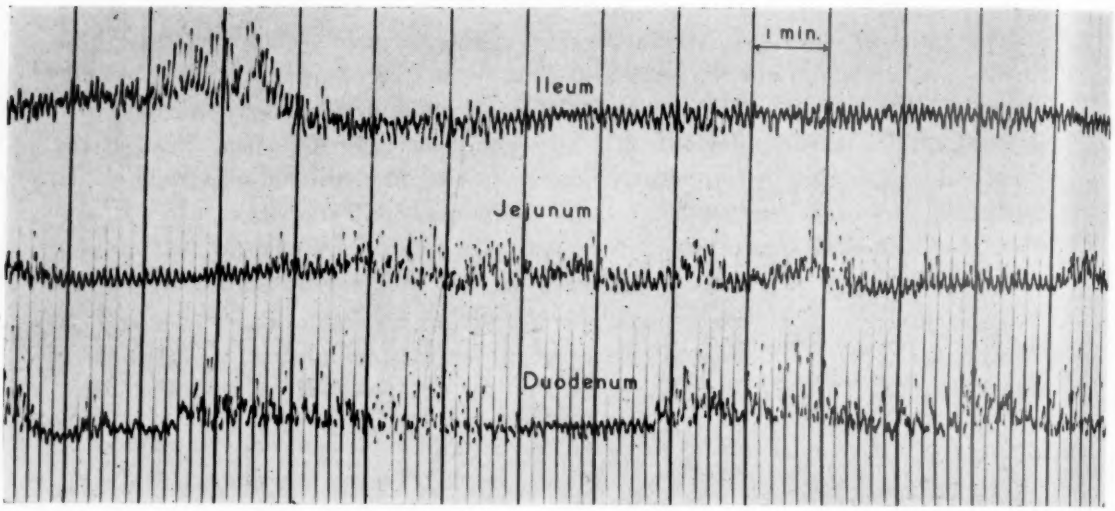


Fig. 1.—Activity of loops of ileum, jejunum, and duodenum one hour after the ingestion of food and before vagotomy.

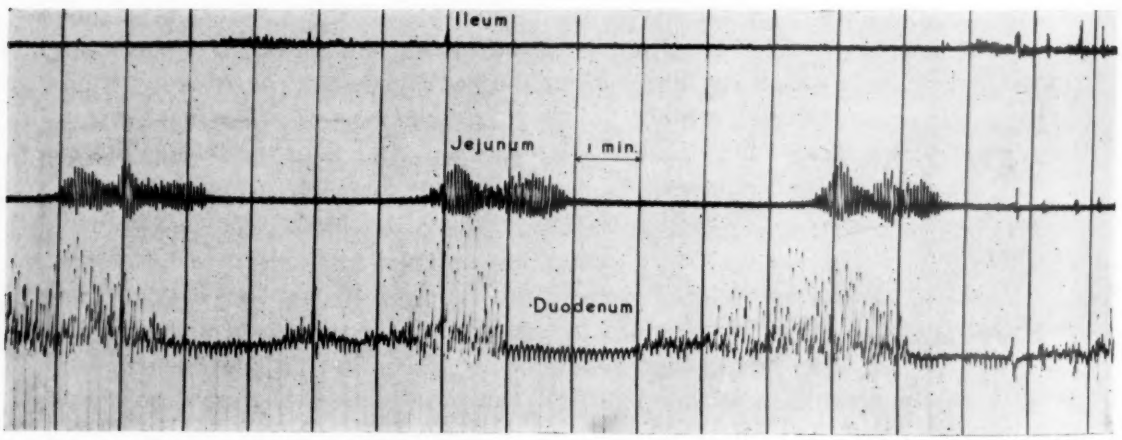


Fig. 2.—Tracings from the same animal as in Fig. 1, one hour after the ingestion of food and after vagotomy. Note the decrease in intestinal activity.

decreased in number and amplitude; the vigor of the activity was decreased in each segment of the intestine, and the period of activity after the meal was prolonged (Figs. 1 and 2).

SUMMARY

Vagotomy does not produce a marked effect on intestinal activity. However, the following differences between the normal and vagotomized animal were

noted. After section of the vagi a longer period of fasting was required for the intestine to become quiescent. The burst of activity which in the normal animal usually occurs at the sight and smell of food appeared to be absent after vagotomy. The feeding reaction in the vagotomized dog was very slightly delayed and the duration was decreased. The peristaltic waves appeared to be less in number, of shorter duration and occurred at longer intervals of time. The periods of rhythmic segmentation were increased, but the rate and gradient phenomenon were unchanged.

It is suggested that these findings are owing (1) indirectly to the effect of vagotomy upon gastric functions, such as delayed emptying time, decrease in acidity, and so forth, and (2) to decrease in tone of the intestine.

REFERENCES

1. Alvarez, W. C.: Sixty Years of Vagotomy; a Review of Some 200 Articles, Gastroenterology **10:** 413-441, 1948.
2. Biebl, Max: Graphische Darnstellung der Darmbewegungen: an der in einem Hautschlauch exventerierten Darmschlinge, Klin. Wchnschr. **9:** 1674-1675, 1930.
3. Douglas, D. M., and Mann, F. C.: An Experimental Study of the Rhythmic Contractions in the Small Intestine of the Dog, Am. J. Digest. Dis. **6:** 318-322, 1939.
4. Mathur, P. D., Grindlay, J. H., and Mann, F. C.: Observations on Duodenal Motility in Dogs With Special Reference to Activity During Vomiting, Gastroenterology **10:** 866-879, 1948.
5. Douglas, D. M., and Mann, F. C.: The Activity of the Lower Part of the Ileum of the Dog in Relation to the Ingestion of Food, Am. J. Digest. Dis. **6:** 434-439, 1939.

CHLOROPHYLL AS AN ADJUNCT IN THE MANAGEMENT OF THE PERMANENT COLOSTOMY

JULIEN M. GOODMAN, M.D., COLUMBUS, OHIO

(From the Department of Surgery, Ohio State University College of Medicine)

PATIENTS with a permanent colostomy usually learn to control it in such a way that embarrassment from an involuntary passage of gas or feces hardly ever occurs. Nevertheless, there is often a period of a number of weeks, during which the patient and his colostomy are "becoming acquainted," so to speak, when an agent to deodorize the colostomy effectively would be very welcome. This is particularly true for patients who are able to resume their usual activities before the colostomy is completely under control.

Interest in this problem was stimulated by the case of a businessman who hesitated to return to his office solely because of the odor which he feared might be noticeable to others. In casting about for a suitable substance to overcome this problem, it seemed that chlorophyll might answer the requirements. Chlorophyll in solution, with a wick as an absorbent, has been widely and effectively used to remove various undesirable odors such as those which may occur in kitchens, public lavatories, or the sick room. Furthermore, numerous investigators have shown that chlorophyll is harmless to living tissue, and some have even claimed that it exerts a beneficial effect upon wound healing.

Chlorophyll has been extensively evaluated by numerous investigators and utilized in the treatment of widely varying pathologic conditions. Gruskin[9] proved chlorophyll to be nontoxic and efficient in the deodorization of drainage tracts communicating with body cavities. Gahan, Kline, and Finkel[7] and also Boehme[1] used chlorophyll solution and chlorophyll in water-soluble bases to treat chronic ulcers. Smith and Livingston[12, 13, 14] proved its usefulness in wound healing by extensive analytical, experimental, and clinical studies, which Lam[10] denied. Chlorophyll has been used to manage dermatophytosis,[15] to control oral sepsis,[8] to maintain wound cleanliness,[6] to treat burns,[5] and to dress suppurative wounds.[2] Cady,[3] and more recently Carpenter,[4] have substantiated its efficacy in promoting wound healing. Moss and associates,[11] in a recent report on the effectiveness of chlorophyll in wound healing and deodorant qualities, found no evidence of retardation of healing by its use, and demonstrated chlorophyll to be a consistent and effective deodorant of foul-smelling wounds.

Preliminary trials demonstrated that 60 mg. of powdered chlorophyll suffice to deodorize the average colostomy for a 24 hour period. Plain dark gelatin capsules* were first prepared which contained 60 mg. of powdered chlorophyll and 300 mg. of powdered activated charcoal. The patient was instructed to insert 1 capsule deep into the colostomy after completion of the morning irrigation and evacuation, and to use an additional capsule if any odor was noted during the day. Twelve patients who were tested on this regime all reported favorably insofar as odor was concerned. The charcoal, however, produced an objectionable discoloration about the colostomy orifice.

Received for publication, Jan. 27, 1950.

*Colostomy capsules were furnished by The Warren-Teed Products Company, Columbus Ohio.

The same 12 patients were given capsules of identical appearance containing only the activated charcoal. Although they were not informed of the substitution, 11 of the 12 volunteered that the capsules had apparently lost some of their effectiveness. On the other hand, a capsule containing 60 mg. of powdered chlorophyll and 360 mg. of colloidal kaolin seemed to be entirely satisfactory. Kaolin alone produced a "weak" effect, according to the patients. It thus appeared to be established that chlorophyll was the most important ingredient in accomplishing deodorization.

The chlorophyll-kaolin mixture has been used by 18 patients with permanent colostomies. No undesirable change in the character of the stool or in bowel habits has been noted by any patient, nor have there been untoward side effects of any description. All of the patients reported favorably upon the performance of these capsules, and in each instance the patient has felt secure enough in their use to resume his daily activities without fear of embarrassment.

CONCLUSIONS

1. Elimination of fecal odors may play a useful role in the early rehabilitation of some patients with a permanent colostomy.

2. A mixture of 60 mg. of powdered chlorophyll and 360 mg. of colloidal kaolin in a plain gelatin capsule will apparently deodorize a colostomy for a number of hours if placed within the colostomy immediately after the morning irrigation and evacuation.

3. The successful use of these capsules by 18 patients with permanent colostomies suggests the desirability of further clinical trial and evaluation.

REFERENCES

1. Boehme, E. J.: Treatment of Chronic Leg Ulcers With Special Reference to Ointment Containing Water Soluble Chlorophyll, Lahey Clin. Bull. **4**: 242, 1946.
2. Bowers, W. J.: Chlorophyll in Suppurative Disease, Am. J. Surg. **73**: 37, 1947.
3. Cady, Joseph B., and Morgan, Winfield S.: Treatment of Chronic Ulcers With Chlorophyll, Am. J. Surg. **75**: 562, 1948.
4. Carpenter, Earnest B.: Clinical Experiences With Chlorophyll Preparations, Am. J. Surg. **77**: 167, 1949.
5. Collings, G. H.: Chlorophyll and Adrenal Cortical Extract in Local Treatment of Burns, Am. J. Surg. **70**: 58, 1945.
6. Finkel, M. D., and Levine, A. J.: Chlorophyll Urea Ointment, Indust. Med. **14**: 730, 1945.
7. Gahan, E., Kline, P. R., and Finkel, T. H.: Chlorophyll in the Treatment of Ulcers, Arch. Dermat. & Syph. **47**: 849, 1943.
8. Goldberg, S. L.: The Use of Water Soluble Chlorophyll in Oral Sepsis, Am. J. Surg. **62**: 117, 1943.
9. Gruskin, B.: Chlorophyll—Its Therapeutic Place in Acute and Suppurative Disease, Am. J. Surg. **49**: 49, 1940.
10. Lam, C. R.: Chlorophyll and Wound Healing, Proc. Am. Federation Clin. Research **2**: 35, 1945.
11. Moss, N. H., Morrow, B. A., Long, R. C., and Ravdin, I. S.: Effectiveness of Chloresium in Wound Healing and Deodorant Effects, J. A. M. A. **140**: 1336, 1949.
12. Smith, L. W., and Livingston, A. E.: Chlorophyll; Experimental Study of Water Soluble Derivatives in Healing, Am. J. Surg. **62**: 358, 1943.
13. Smith, L. W.: Effect of Water Soluble Chlorophyll Derivatives and Other Agents Upon the Growth of Fibroblasts in Tissue Culture, J. Lab. Clin. Med. **29**: 241, 1944.
14. Smith, L. W., and Livingston, A. E.: Wound Healing; An Experimental Study of Water Soluble Chlorophyll Derivatives in Conjunction With Various Antibacterial Agents, Am. J. Surg. **67**: 30, 1945.
15. Wallace, G. I., Day, J. K., and Moorman, H. E.: Chlorophyll Ointment in Treatment of Dermatophytosis of Feet and Similar Lesions, Arch. Dermat. & Syph. **49**: 127, 1944.

THE EFFECTS OF HYPOCHLOREMIA UPON RENAL FUNCTION IN SURGICAL PATIENTS

IRVING M. ARIEL, M.D.,* AND FLETCHER MILLER, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Medical School)

INTRODUCTION

THE frequent occurrence of nitrogen retention as a complication of gastrointestinal obstruction has evoked various theories to explain the extrarenal azotemia. Some believe it is the result of renal damage,[1-4] probably from the liberation of toxins.[1, 2, 5] Others, however, ascribe the azotemia directly to an associated hypochloremia,[6, 7] alkalosis,[8-10] or dehydration.[11-13]

This investigation was undertaken to study renal function, measuring renal plasma flow, the rate of glomerular filtration, and the secretory ability of the tubules in patients who manifested upper gastrointestinal obstruction and who developed hypochloremia during their clinical courses. Renal functions were depressed in the patients so studied. Therefore, it seemed pertinent to note the effects of hypochloremia per se upon kidney function. Hence subjects were rendered hypochloremic experimentally and renal clearances performed. The results of these measures form the subject of the present communication.

PROCEDURE

Renal clearances were performed upon three patients, each of whom developed hypochloremia during the clinical course. The renal tests were repeated usually after replacement therapy had corrected the hypochloremia.

In three additional patients, chloride deprivation was produced by the continuous withdrawal of gastric contents through an indwelling gastric tube attached to gastric suction. In the first two patients, gastric secretion was stimulated by the subcutaneous injection of 0.5 mg. of histamine three times per day. In the third patient gastric secretion was stimulated by the oral ingestion of 30 ml. of 7 per cent ethyl alcohol every four hours during waking hours.

An average of four to six days on the gastric aspiration regime was required to render the patients hypochloremic. During this period they were permitted to eat a salt-free diet with the gastric tube clamped for one hour after each meal. Each patient was given an adequate amount of fluid intravenously, as 5 per cent dextrose in distilled water, in an attempt to avoid the factor of dehydration.

As the patients developed hypochloremia, they generally suffered from lethargy, anorexia, nausea, increased irritability, and at times abdominal pain. After the renal clearance tests had been performed the patients were given

Aided by the American Cancer Society.
Received for publication, Nov. 15, 1949.
Present address: Pack Medical Group, New York, N. Y.

from 13.5 Gm. to 27 Gm. of sodium chloride as normal saline solution intravenously each day until the serum chlorides were normal. This was accomplished usually in two to three days and renal clearance studies were repeated.

No other metabolic irregularities were present in any of the patients, except in two, cases 1 and 6, who manifested anemia.

METHODS

The patients were maintained in a basal state on the day the renal tests were performed. Water was permitted ad lib. to insure adequate diuresis.

Kidney function tests were performed by the multiple period methods devised by H. W. Smith.[14, 15] Glomerular filtration rate was determined as the sodium thiosulphate clearance, and the effective renal plasma flow as the sodium para-aminohippurate (PAH) clearance. Tubular function was studied by the saturation technique, that is, the maximal tubular secretory capacity for sodium para-aminohippurate (Tm PAH). Analyses were performed upon plasma filtrates according to the method of Fujita and Iwatake, and upon diluted aliquots of catheterized urine as described by Goldring and Chasis.[15] Para-aminohippurate was determined by the method described by Smith and associates.[16] Sodium thiosulfate was performed by the method of Gilman and co-workers.[17]

The values expressed usually represent the average of three clearance periods, except occasionally, when technical difficulties precluded obtaining data for the three clearances. All results are corrected in proportion to surface area, and the final figure is expressed in terms of the surface area of ideal man (1.73 square meters).

Normal effective renal plasma flow is reported at 697 ± 135.9 ml. per minute for males and 594 ± 102.4 ml. per minute for females.[18]

Glomerular filtration rate in the normal male is 131 ± 21.5 ml. per minute, and for the normal female it is 117 ± 15.6 ml. per minute.[18] The normal value for Tm PAH is 77.5 ± 12.9 mg. per minute for both sexes.[18] The patients were weighed each morning.

Serum chlorides were determined by the method of Schales and Schales.[19] The normal range is between 100 and 106 meq. per liter.

The carbon dioxide combining power of the serum was ascertained by the technique of Van Slyke and Cullen.[20] Normally, this ranges from 22 to 27 meq. per liter.

Serum proteins were determined by the technique of Weichselbaum.[21]

Blood urea nitrogen was measured by the method described by Peters and Van Slyke,[22] and adopted for the Evelyn colorimeter. Hematocrit values were obtained by centrifuging samples of whole blood at 3,000 revolutions per minute for 30 minutes.

RESULTS

The course of each patient is presented separately.

Group I. Patients Who Developed Hypochloremia During Their Clinical Courses

CASE 1.—The patient, H. O., a 68-year-old white man, had symptoms consisting of loss of appetite, weakness, and a thirty-pound weight loss of three months' duration. Physical examination on admission to the hospital revealed a weak, pale man. A roentgenologic study of the gastrointestinal tract demonstrated an almost complete obstruction of the stomach by a large meniscus-shaped filling defect involving the lesser curvature.

The laboratory findings on admission were not remarkable. The gastric contents contained 68 degrees of free acid on histamine stimulation. The hemoglobin was 12 Gm. per cent. Serum chloride was 94 meq. per liter and the carbon dioxide combining power 25 meq. per liter.

Because of the marked gastric distention the patient was treated with continuous gastric suction by means of an indwelling stomach tube. Copious quantities of gastric secretion were aspirated, and, despite the intravenous administration of large quantities of chloride-containing fluid averaging 19 Gm. of sodium chloride daily, he developed hypochloremia and alkalosis (Chart 1). This was eventually corrected by withdrawal of the gastric tube and continued administration of sodium chloride. Ten days after admission, at which time the blood chemistries were normal, a subtotal gastrectomy was performed for a benign gastric ulcer.

Renal clearance studies were performed on the fifth day after admission, at which time the serum chloride revealed 93 meq. per liter and the carbon dioxide combining power was 36 meq. per liter (Chart 1).

Since the renal clearance tests were performed after corrective fluid therapy had been instituted and the blood chemistries were improving, the possibility exists that the renal functions might have been depressed further when the patient was in a more severe state of hypochloremia.

The tests were repeated five days later, at which time the serum chloride was 98 meq. per liter and the carbon dioxide combining power 22 meq. per liter. There was improvement in the glomerular filtration rate, which increased from 111.6 ml. per minute, when the patient was hypochloremic, to 145 ml. per minute as the blood chemistries approached normal. Renal plasma flow increased somewhat also as the hypochloremia was corrected.

Immediately following surgery, renal plasma flow increased still higher. The renal plasma flow was 543.6 ml. per minute when the patient was hypochloremic but rose to 622.3 ml. per minute subsequent to surgery when the blood chemistries were normal.

CASE 2.—The patient, L. S., a 50-year-old white man, presented a history of postprandial substernal burning of ten months' duration, and dysphagia with inability to swallow solid food of one month's duration. There had been a recent weight loss of twenty pounds and increasing fatigability since the onset of symptoms.

A diagnosis of carcinoma of the esophagus was established by esophagoscopic examination and biopsy. The pertinent features pertaining to the fluid exchange and the essential laboratory findings are presented in Chart 2.

It may be noted that on admission the serum chloride was 100 meq. per liter. The carbon dioxide combining power was 25 meq. per liter, and the blood urea nitrogen was 11 mg. per cent.

Because of obstruction and signs of gastric distention he was treated by continuous gastric aspirations through an indwelling stomach tube, and was operated upon six days after admission through an abdominal and a right thoracic incision. A partial esophagectomy was performed, followed by an esophagogastrostomy.

Subsequent to surgery, the patient's course was marked by a hypochloremia of 76 meq. per liter (Chart 2).

Renal clearance studies performed while the patient was hypochloremic revealed that the renal plasma flow was 346.4 ml. per minute and the glomerular filtration rate 73.9 ml. per minute. The filtration fraction was 21.1.

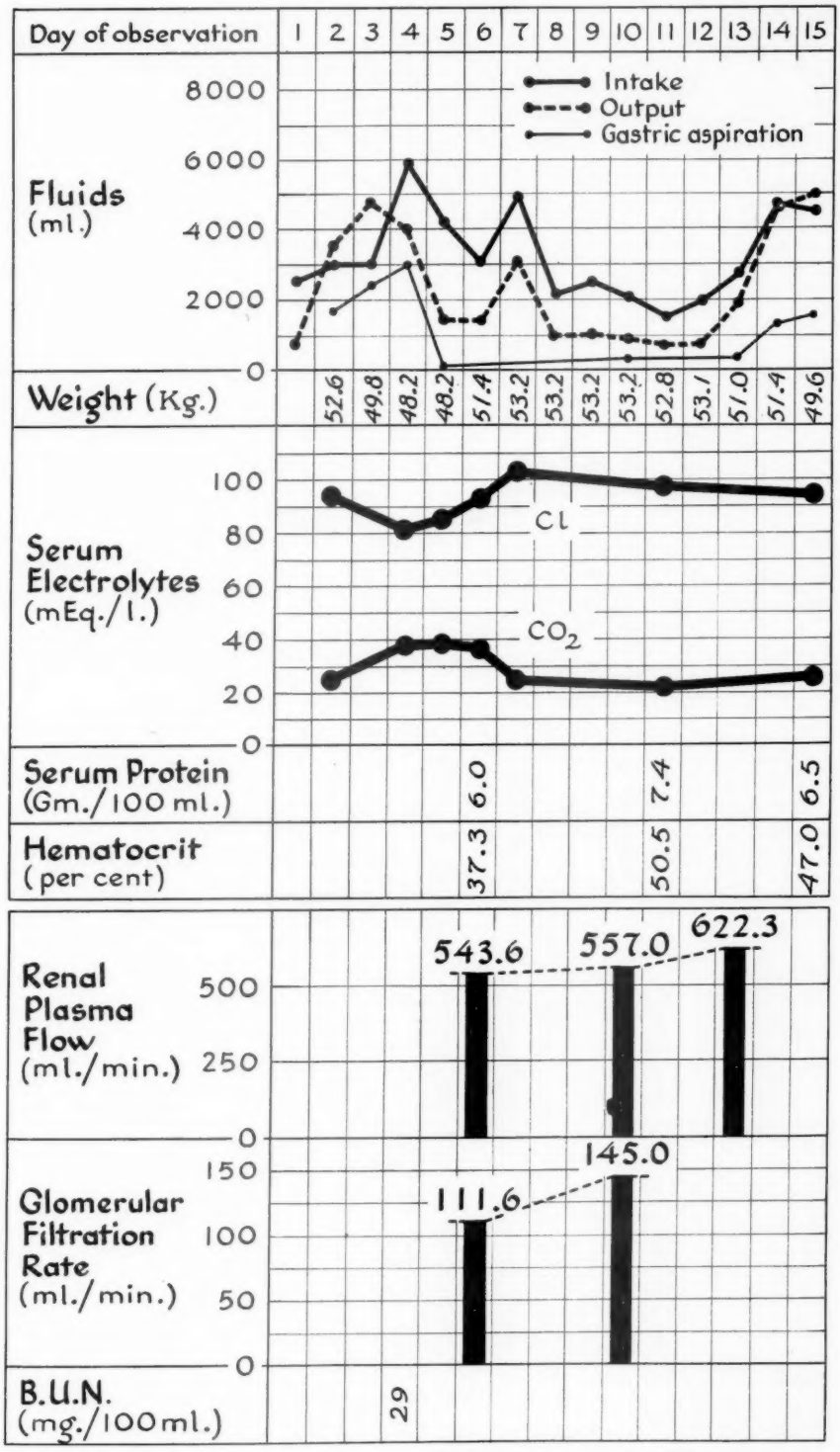


Chart 1 (Case 1).—Effects of serum chloride concentration upon renal plasma flow and glomerular filtration rate.

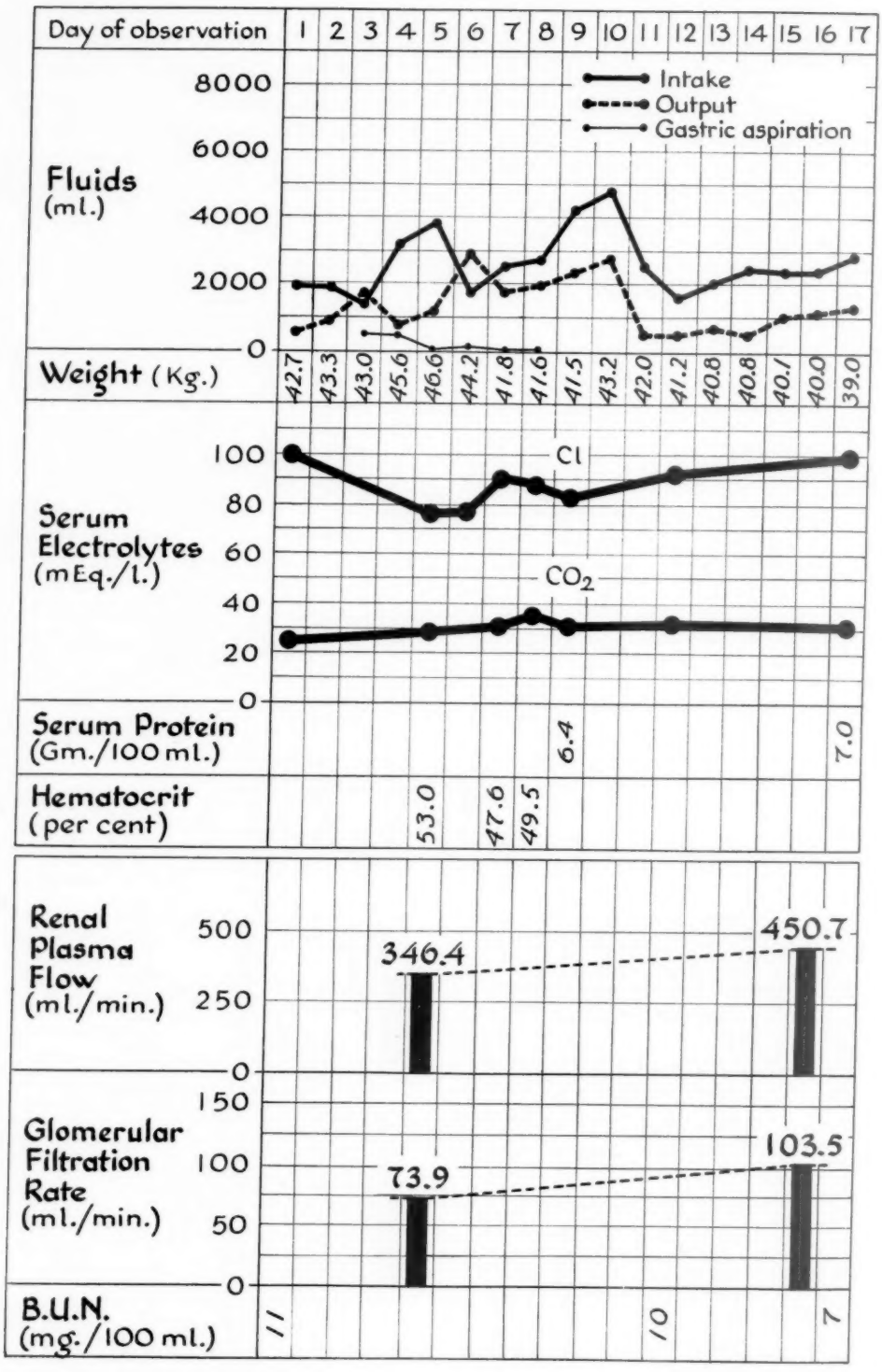


Chart 2 (Case 2).—Improvement in renal plasma flow and glomerular filtration rate after correction of hypochloremia.

After the hypochloremia had been corrected, the renal plasma flow increased to 450.7 ml. per minute, and an increase in the glomerular filtration rate to 103.5 ml. per minute was observed.

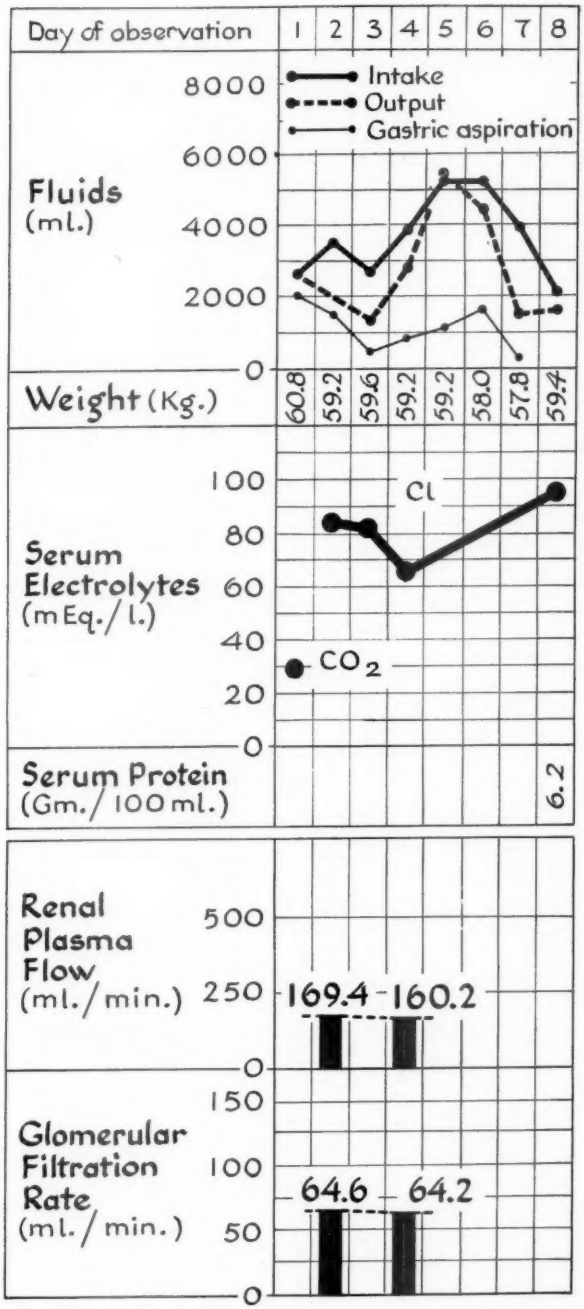


Chart 3 (Case 3).—Demonstrating depression of renal flow and glomerular filtration rate while patient was in a state of hypochloremia.

CASE 3.—B. B., a 51-year-old white man, was admitted to the University Hospitals with a five-month history of severe vomiting, hematemesis, gnawing epigastric pain, and a loss of thirty pounds in weight. Roentgenograms revealed a large, infiltrating, stenosing lesion in the distal one-half of the stomach which was diagnosed as carcinoma.

On admission to the hospital, the laboratory studies were as follows. Hemoglobin was 15.2 Gm. per cent, hematocrit 45.5 per cent, and the carbon dioxide combining power 29 meq. per liter, although the serum chloride was depressed to 84 meq. per liter. The patient was operated upon seven days after admission and a subtotal gastrectomy and partial transverse colectomy were performed. Despite the presence of hypochloremia during the immediate postoperative phase (serum chloride was 64 meq. per liter), he made an uneventful recovery and was discharged on the seventh postoperative day, at which time the hypochloremia had been corrected (Chart 3).

Renal clearance studies performed during the immediate pre- and postoperative states, when the patient was hypochloremic, demonstrated noteworthy decreases in renal plasma flow (169.4 and 160.2 ml. per minute) and glomerular filtration rate (64.6 and 64.2 Gm. per minute). Tm PAH was at the lower limit of normal (63.7 mg. per minute) on one occasion and subnormal (55 mg. per minute) when the test was performed postoperatively at the time the serum chloride was 64 meq. per liter.

Each of these three patients revealed depressed renal function when he was hypochloremic. When the hypochloremia was corrected, improvements in renal clearances were observed.

Group II. Patients Who Were Rendered Hypochloremic Experimentally to Note the Effects Upon Renal Clearance

CASE 4.—L. G., a 53-year-old white man, was admitted to University Hospitals because of severe hematemesis due to a duodenal ulcer.

Two days after admission a salt depletion regime was instituted by the continuous aspiration of gastric secretion stimulated by histamine. After seven days of salt withdrawal, the serum chloride had descended from an admission value of 101 meq. to 80 meq. per liter, and the carbon dioxide combining power was 38 meq. per liter, having risen from 26 meq. per liter. During the hypochloremic state the renal plasma flow was 461 ml. per minute, having decreased 36 per cent from the prehypochloremic state of 724.6 ml. per minute.

A mild decrease in glomerular filtration rate was observed also, declining from 126 ml. per minute during the prehypochloremic state to 105 ml. per minute when the patient was hypochloremic. A slight increase in the filtration fraction from 17.4 to 22.8 occurred during hypochloremia. This patient further demonstrated a depression of the tubular excretory function, which had diminished from the value of 80.7 mg. per minute on admission to 59.8 mg. per minute after the patient had been rendered hypochloremic. All determined renal functions again returned to higher levels when the hypochloremia had been corrected during the postoperative phase (Chart 4).

CASE 5.—C. B., a 49-year-old white man, was admitted to University Hospitals with a history of melena of fifteen days' duration and a weight loss of fifteen pounds during the preceding month. A diagnosis of carcinoma of the rectosigmoid was established by histologic examination of the sigmoidal lesion.

Five days after admission the patient was placed upon a salt depletion regime with the continuous aspiration of gastric contents stimulated by 0.5 mg. histamine three times per day.

The pertinent data concerning this patient are presented in Chart 5. It may be noted that the serum chloride decreased from an admission value of 108 meq. per liter to a low level of 79 meq. per liter. There was an associated increase in the carbon dioxide combining power from 27 meq. per liter to 35 meq. per liter. The gastric secretion during the first two days of depletion contained 6.2 Gm. of sodium chloride per liter. During the three last days of the depletion regime, during which time hypochloremia persisted, the gastric contents contained 5.9 Gm. of sodium chloride per liter. This demonstrates that the quantity of chloride within the gastric secretion is not dependent upon the serum chloride concentration.[10] The quantity of chloride in the urine decreased rapidly as the

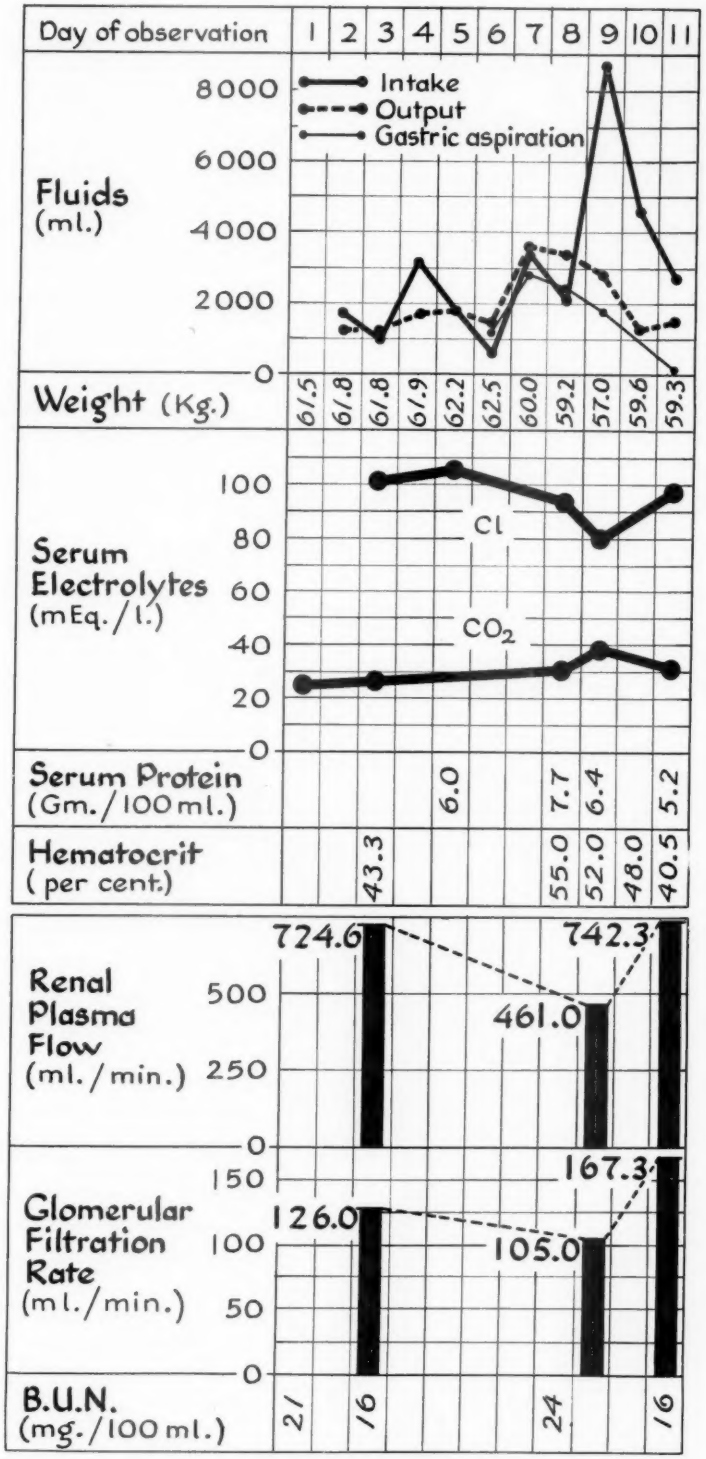


Chart 4 (Case 4).—Demonstrating the effects of induced hypochloremia on renal plasma flow and glomerular filtration rate and improvement of renal functions with correction of hypochloremia.

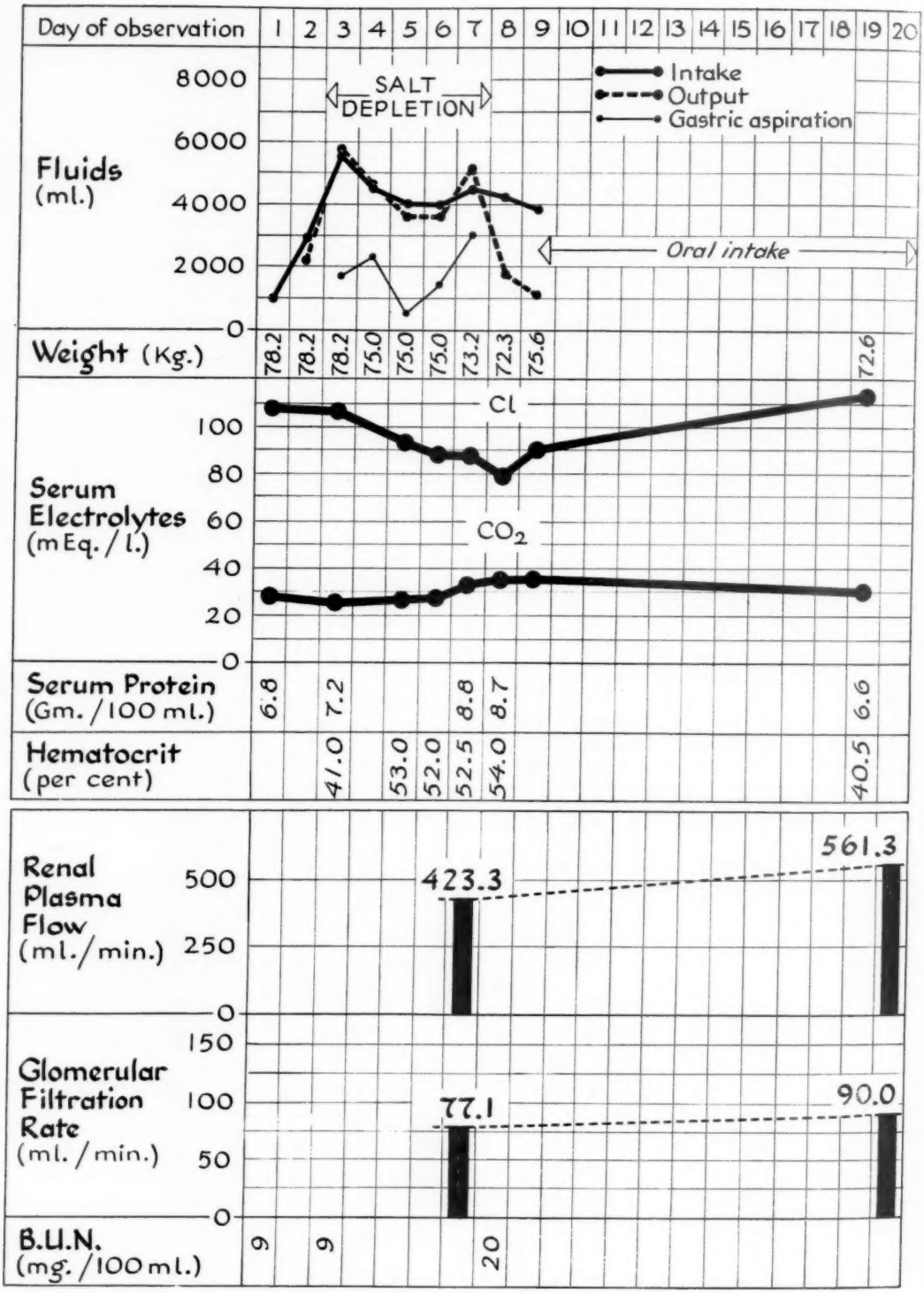


Chart 5 (Case 5).—Illustrating effects of hypochloremia on certain renal functions.

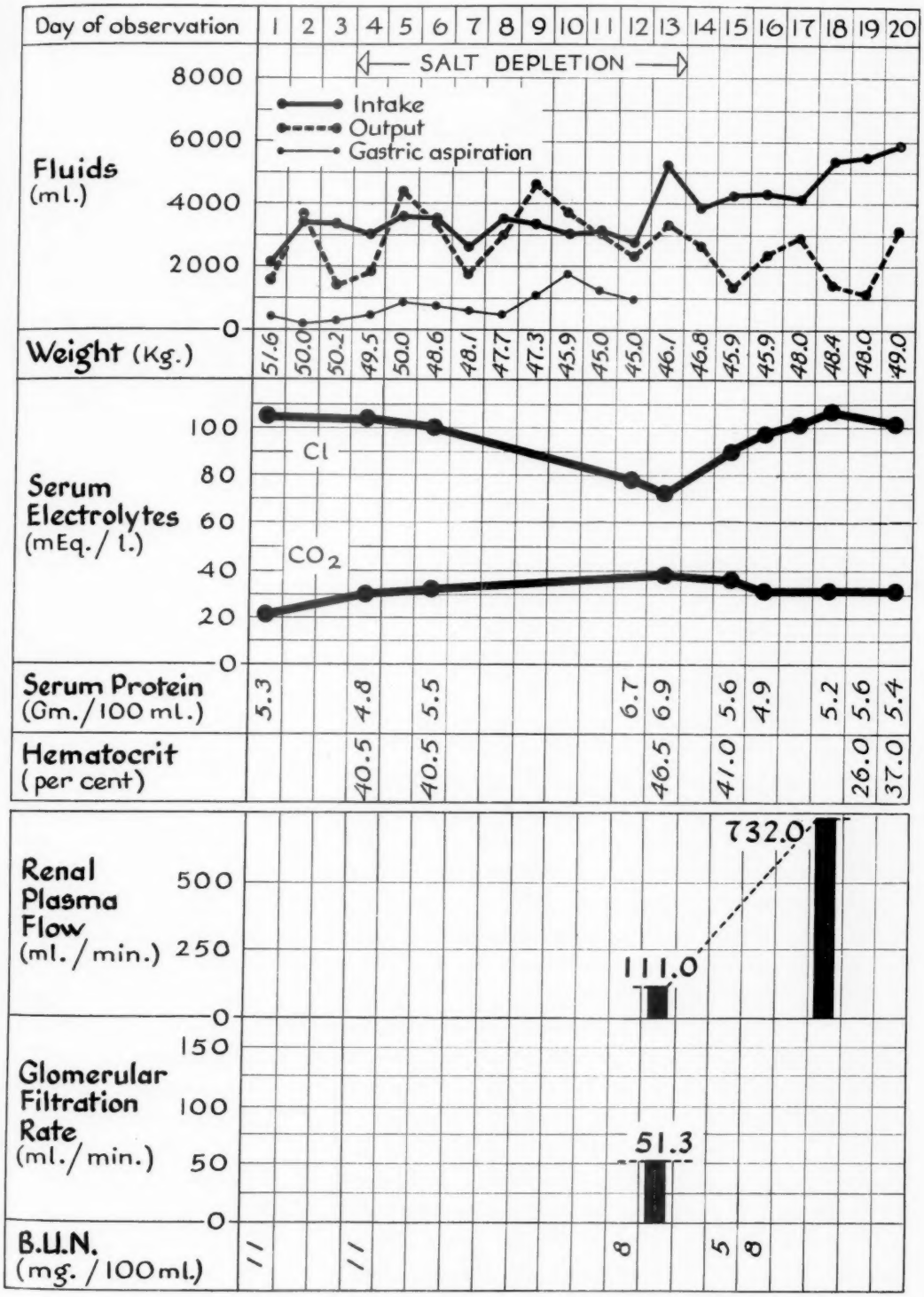


Chart 6 (Case 6).—Demonstrating marked alterations in renal plasma flow resulting during induced alterations in serum chloride concentration.

depletion state was induced. At the onset of the test the urine contained 5.9 Gm. of sodium chloride per liter, whereas toward the completion of the test, when the plasma chlorides had descended to 79 meq. per liter, the concentration of urine sodium chloride was 0.2 Gm. per liter.

It is estimated that 54 Gm. of salt were withdrawn from the patient during the six days of gastric suction. A significant weight loss of 6 kg. developed during the salt depletion regime, despite the intravenous administration of copious quantities of fluid.

When the patient was hypochloremic, the renal plasma flow was depressed to 423.3 ml. per minute, which increased to a normal value of 561.3 ml. per minute when the hypochloremia was corrected. The glomerular filtration rate was likewise depressed to the subnormal value of 77.1 ml. per minute. Although improvement in glomerular filtration rate occurred with correction of the blood chemistry (90.0 ml. per minute) it did not reach a normal level.

CASE 6.—V. C., a 65-year-old white woman, was admitted to the University Hospitals with large bowel obstruction due to an adenocarcinoma of the splenic flexure. Five days after admission, she was placed on a salt depletion regime by continuous aspiration of the gastric contents through an indwelling stomach tube. Gastric secretion was stimulated by the oral ingestion of 30 ml. of 7 per cent ethyl alcohol every four hours. An adequate fluid intake was maintained on this regime for nine days, during which time 3,300 ml. of gastric juice were aspirated, containing an average of 4.4 Gm. of sodium chloride per liter. The patient's serum chlorides decreased from 105 meq. per liter to 72 meq. per liter. The carbon dioxide combining capacity rose from 21 meq. per liter to 38 meq. per liter. When the patient was hypochloremic and alkalotic, renal function studies revealed that the renal plasma flow was the low value of 111 ml. per minute and glomerular filtration rate was 51.3 ml. per minute. Renal clearance studies performed when the serum chloride value was normal demonstrated a marked improvement in renal plasma flow to 732 ml. per minute (Chart 6).

DISCUSSION

The data herein presented demonstrate that all patients suffering from hypochloremia of this series have depressed renal plasma flow and a decreased rate of glomerular filtration. Alterations in filtration fraction were not remarkable, but the secretory capacity of the tubules was subnormal in two of the five instances where determinations were performed. Marked increases in the blood urea nitrogen did not accompany the hypochloremic state but moderate to severe alkalosis was usually a concomitant feature.

The association between hypochloremia and renal dysfunction has been discussed since 1904, when Nazari described calcium deposition in the kidneys of patients dying from pyloric stenosis.[23] Since then, reports of pathologic changes in the kidneys by Brown, Eusterman, Hartman, and Rowntree,[2] who called the pathologic entity "toxic nephritis," and Cook,[3] Zeman,[24] Martz,[4] Gomori,[13] and Nicol[25] have focused attention upon the relationship between pyloric obstruction and renal damage. As a result, various theories have been promulgated to explain the pathogenesis of the renal lesions.

Certain investigators believe the renal damage results from the liberation of toxins,[2] probably end products of protein catabolism.[5]

The observation that hypochloremia causes nitrogen retention, even in the absence of gastrointestinal obstruction,[6] has led to the belief that chloropenia diminishes kidney function and causes an increase of the blood nonprotein nitrogen.[7]

Also, azotemia associated with alkalemia produced by the ingestion of alkali has been ascribed to a concomitant hypochloremia, and improvement in renal function occurs with correction of the chloropenia by sodium chloride administration.[27]

The mechanism by which a decreased serum chloride evokes an increased blood urea nitrogen has been commented upon but remains enigmatic. Some of the explanations offered are as follows. The increased blood urea nitrogen is a means whereby the body conserves urea by reabsorbing it through the renal tubules to substitute for the depleted plasma chloride to help maintain osmotic pressure.[7] This explanation is unlikely, however, because urea diffuses freely to all body tissues (both intra- and extracellular) and hence would not aid materially in maintaining osmotic pressure of the plasma or the extracellular compartment.

The explanation has been advanced that hypochloremia per se damages the kidney[27] or causes functional alterations with depressions of urea clearance[28] and creatinine, sucrose, and insulin clearances.[29]

Other investigators present evidence that the essential factor which disrupts renal function is not the hypochloremia but an associated dehydration.[11] Dehydration may induce azotemia by hemoconcentration, increasing protein catabolism with the liberation of increased quantities of nonprotein nitrogen,[10] or diminishing kidney function by decreasing the rate of circulation,[10, 30] or depressing the filtration rate.[13, 29]

In order to substantiate the hypothesis that dehydration is the responsible agent, Kirsner[27] has produced hypochloremia experimentally without azotemia and has shown that in severe acute alkalosis without depletion of fluid no impairment of urea and creatinine clearance occurred. His data, however, are not conclusive in vindicating hypochloremia as an etiological factor in diminishing renal function.

When the electrolytic imbalance is corrected, renal function returns to normal. The return of renal function to normalcy may be rapid, as McCance and Widdowson,[29] using creatinine, insulin, and other clearances, and Cope,[31] utilizing urea kidney clearances, have demonstrated, or it may be delayed for several months as observed by Berger[32] and Jeghers and Lerner.[33]

It appears accordingly that the kidney changes are reversible and suggests the alterations are of a functional nature in response to altered chemical changes and that structural damage does not necessarily accompany or cause the functional derangement.

The results of this investigation substantiate the reports that hypochloremia induced by the withdrawal of salt-containing fluid depresses renal function. The pathogenesis of the hypochloremia in the two groups of this series was essentially the same, namely, withdrawal of chloride-containing gastric juice. The data demonstrate that depletion of chloride-containing fluid is the etiological factor for the production of the renal depression and that other factors, such as absorption of toxins, are not necessary to explain renal dysfunction. No relationship was observed between the degree of hypochloremia and the suppression of renal clearance.

TABLE I. EFFECT OF HYPOCHLOREMIA UPON KIDNEY FUNCTION

	HYPOCHLOREMIC PERIOD					POSTHYPOCHLOREMIC PERIOD (NORMAL SERUM CHLORIDE LEVELS)				
PATIENT	SERUM CL. (MEQ. PER LITER PER MINUTE)	RENAL PLASMA FLOW (ML. PER MINUTE)	GLOMERULAR FILTRATION RATE (ML. PER MINUTE)	FILTRATION FRACTION	TM. PAH (MG. PER MINUTE)	SERUM CL. (MEQ. PER LITER PER MINUTE)	RENAL PLASMA FLOW (ML. PER MINUTE)	GLOMERULAR FILTRATION RATE (ML. PER MINUTE)	FILTRATION FRACTION	TM. PAH (MG. PER MINUTE)
Group I. Hypochloremia Developed During Clinical Course										
1. H. O.	93	543.6	111.6	21.1	68.5	98	557	145	20.6	68.8
2. L. S.	76	346.4	73.9	21.1		99	450.7	103.5	22.3	
3. B. B.	84	169.4	64.6	38	63.7					
	64	160.2	64.2	40	55					
Group II. Hypochloremia Induced Experimentally by Chloride Depletion										
						97	742.3	167.3	22.4	66.4
4. L. G.	80	461	105	22.8	59.8	101*	724.6	126	17.4	80.7*
5. C. B.	79	423	77.1	20	78.3	113	561.3	90	16	71.8
6. V. C.	72	111	51.3			106	732			

*Studies performed before hypochloremia was induced.

In prolonged cases of severe gastric obstruction or prolonged hypochloremia, other factors may contribute to cause a damaged kidney with evidence of pathologic anatomy.[2, 3]

These investigations further demonstrate the nature of the kidney abnormalities, namely, decreased effective renal plasma flow, decreased glomerular filtration rate, and in certain instances decreased efficiency of the tubular excretory mechanism (Table I). Estimation of renal blood flow from hematocrit values demonstrates that improvement of the blood flow of the kidneys occurred also in all instances where hypochloremia was corrected (Table II).

It is of interest that marked azotemia did not result from the diminished renal function, and whether prolongation of the hypochloremia would have resulted in increased nonprotein nitrogen is problematical.[1]

The rapid improvement in the observed renal functions after correction of the abnormal electrolytic balance is further evidence that the altered physiochemical status was responsible for the renal dysfunction. The values for the renal plasma flow, glomerular filtration rate, and tubular mass (Tm PAH) did not always return to a normal value, and it is probable that a longer period of time was necessary for the kidneys to regain normal function.[32, 33]

It is beyond the scope of these data to distinguish whether hypochloremia per se or associated dehydration produced the renal alterations. That dehydra-

TABLE II. EFFECT OF HYPOCHLOREMIA UPON RENAL BLOOD FLOW

PATIENT	PERIOD OF HYPOCHLOREMIA (RENAL BLOOD FLOW IN ML. PER MINUTE)	HYPOCHLOREMIA CORRECTED (RENAL BLOOD FLOW IN ML. PER MINUTE)
1	868	1,193
2	736	
4	959	1,247
5	893	959
6	205.5	989

tion did occur is suggested by the weight loss of all patients rendered hypochloremic. The withdrawal of gastric contents which contain, in addition to hydrochloric acid, sodium,[34] and to a lesser extent potassium, results in loss of the cations with a depletion of total plasma electrolytes.[34] In the absence of sufficient quantities of osmotically active ions fluid cannot be retained, and, despite the adequate administration of water, dehydration occurs.[34] The paradoxical state of an increased urine output in the presence of water need develops and a dehydration, not of deprivation but of depletion, results.

Volume studies performed upon one patient (Case 6) this series, when hypochloremia existed, revealed a decrease in blood volume, plasma volume, and extracellular space, which condition was corrected solely by the administration of saline-containing fluid. Hyponatremia and slight diminution of serum potassium accompanied the chloropenia (Table III).

TABLE III. VOLUME STUDIES* DURING HYPOCHLOREMIA

	SERUM ELECTROLYTES (MEQ. PER LITER)							
	CL	CO_2 COMBINING POWER	NA+	K+	BLOOD VOLUME† (LITERS)	PLASMA VOLUME‡ (LITERS)	EXTRACELLULAR SPACE§ (LITERS)	WEIGHT OF PATIENT (KG.)
Period of normal blood chloride	104	30	148	3.4	—	—	—	50.2
Hypochloremia	72	38	127	2.5	3.8	2.16	6.9	46.1
Hypochloremia corrected	106	31	153	3.7	4.8	3.5	9.3	48.4

*These volume studies were performed upon a patient (Case 6) at the same time renal clearance tests were performed.

†Whole blood volume was computed from hematocrit values.

‡Plasma volume was measured by Evans blue dye.

§Extracellular space was measured by sodium thiocyanate.

Accordingly it is important from a clinical standpoint to recall that in all cases of hypochloremia which result from loss of body fluids (such as loss of gastric juice) a concomitant dehydration of depletion develops despite the administration of copious quantities of ionic-free fluids in addition to an abnormal distribution of the available fluid.[35] In such conditions, renal plasma flow, glomerular filtration rates, and, in some instances, tubular excretory mechanisms are depressed.

Within recent years, as a result of observations concerning the dangers of excess saline administration to surgical patients,[36, 37] certain surgeons have leaned in the opposite direction and tend to maintain their patients hypochloremic. The observations herein described focus attention to the abnormal fluid distribution and depression of renal functions which are associated with hypochloremia and emphasize the desirability of maintaining as normal a postoperative physiologic balance as possible in the patient.

SUMMARY AND CONCLUSIONS

1. Renal plasma flow and glomerular filtration rates were depressed in six patients with hypochloremia. Three of the patients suffered from upper gastrointestinal obstruction and developed hypochloremia during their hospital course.

Three additional patients were rendered hypochloremic experimentally by the continuous withdrawal of gastric juice and their renal clearances simulated those in the patients whose hypochloremia developed during therapy for gastric obstruction.

The altered renal function is the result of an abnormal physiochemical balance.

2. Improvement occurred in effective renal plasma flow and glomerular filtration rate when chloropenia was corrected by the intravenous administration of isotonic solutions of sodium chloride.

After correction of hypochloremia, although improvement occurred, in two of six observations the renal plasma flow did not reach normal value and in two of five instances glomerular filtration rates remained subnormal.

Accordingly, in certain instances depressed renal function may persist for a variable period after correction of the diminished serum chloride.

3. The excretory capacity of the tubules (Tm PAH) was subnormal in two of five determinations during hypochloremia. In the one instance in which a depressed Tm PAH existed during hypochloremia and studies were performed after correction of hypochloremia, improvement of tubular excretion occurred. Tm PAH accordingly, is not uniformly depressed by hypochloremia.

4. These data do not contribute in distinguishing whether or not hypochloremia per se, a concomitant dehydration, or a combination of factors contributes to the depression of renal function.

5. Certain clinical implications of these observations as they pertain to the surgical patient are discussed.

REFERENCES

1. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**: 365, 1923.
2. Brown, G. E., Eusterman, C. B., Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction; Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**: 425, 1923.
3. Cook, A. M.: Calcification of the Kidneys in Pyloric Stenosis, Quart. J. Med. **2**: 539, 1933.
4. Martz, H.: Renal Calcification Accompanying Pyloric and High Intestinal Obstruction, Arch. Int. Med. **65**: 375, 1940.
5. McQuarrie, I., and Whipple, G. H.: Renal Function Influenced by Intestinal Obstruction, J. Exper. Med. **29**: 397, 1919.
6. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**: 407, 1930.
7. Blum, L., Grabar, P., and Van Caulaert, C.: L'azoteme par marque de sel, Presse méd. **36**: 1411, 1928.
8. Stieglitz, E. J.: Histologic Hydrogen-Ion Studies of the Kidney, Arch. Int. Med. **33**: 483, 1924.
9. Jordan, S. M.: Calcium Chloride and Carbon Dioxide Content and Venous Blood in Cases of Gastroduodenal Ulcer Treated With Alkalis, J. A. M. A. **87**: 1906, 1926.
10. Kirsner, J. B., and Knowlton, K.: Acid-Base Balance, Renal Function and Gastric Secretion During Hypochloremia in the Dog, J. Clin. Investigation **20**: 303, 1941.
11. Kerpel-Fronius, E., Butler, A.: Salt and Water Losses in Druretin Druresis and Their Relation to Serum Non-Protein Nitrogen and Electrolyte Concentrations, J. Exper. Med. **61**: 157, 1935.
12. Clausen, J.: Studies on the Relation Between Hyperazotemia and Sodium Chloride Deficiency, Acta med. Scandinav. **91**: 523, 1937.
13. Gomori, P., and Frenreisz, S.: Influencing Hypochloremic Azotemias With Hypertonic and Physiological Sodium Chloride Solutions, Acta med. Scandinav. **92**: 503, 1937.

14. Smith, H. W.: Lectures on the Kidney, Porter Lectures; Series IX, University Extension Division, University of Kansas, Lawrence, Kan., 1947.
15. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, 1944, The Commonwealth Fund, p. 195.
16. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M.: Renal Clearances of Substituted Hippuric Acid Derivatives and Other Aromatic Acids in Dog and Man, J. Clin. Investigation **24:** 338, May, 1945.
17. Gilman, A., Philips, F. S., Koelle, E.: The Renal Clearance of Thiosulfate With Observations on Its Volume Distribution, Am. J. Physiol. **146:** 348, 1946.
18. Chasis, H., and Redish, J.: Evolution of Renal Function in Man, The CAMSI Journal **4:** 1, 1945.
19. Schales, O., and Schales, S.: A Simple and Accurate Method for the Determination of Chloride in Biological Fluids, J. Biol. Chem. **140:** 879, 1941.
20. Peters, J., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 2, Baltimore, Md., 1932, Williams & Wilkins Company, p. 251.
21. Weichselbaum, T. E.: Accurate and Rapid Method for Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path., Tech. Sect. **10:** 40, 1946.
22. Peters, J., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 2, Baltimore, Md., 1932, Williams & Wilkins Company, pp. 557.
23. Nazari, A.: Alterazioni renali nella tetania gastrica, Policlin. **11:** 146, 1904. Quoted by Kirshner, J., and Knoulton, K.[10]
24. Zeman, F. D., Friedman, W., and Mann, L. T.: Kidney Changes in Pyloric Obstruction, Proc. N. York Path. Soc. **24:** 41, 1924.
25. Nicol, B. M.: The Renal Changes in Alkalosis, Quart. J. Med. **9:** 91, 1940.
26. Blum, L., Grabar, P., and Van Caulaert, C.: L'azotémie par manque de sel; son mécanisme, Ann. de méd. **25:** 34, 1929.
27. Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis, J. A. M. A. **116:** 384, 1941.
28. Landis, E. M., Elsom, K. A., Bott, P. A., and Shiels, E.: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, J. Clin. Investigation **14:** 525, 1935.
29. McCance, R. A., and Widdowson, E. M.: The Secretion of Urine in Man During Experimental Salt Deficiency, J. Physiol. **91:** 222, 1937.
30. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, 1934, Lea & Febiger, p. 40.
31. Cope, C. L.: Base Changes in Alkalosis Produced by the Treatment of Gastric Ulcer With Alkalis, Clin. Sc. **2:** 287, 1936.
32. Berger, E. H.: Improvement of Kidney Function in Alkalosis, Northwest Med. **36:** 125, 1937.
33. Jeghers, H., and Lerner, H. H.: The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer: Report of Cases with a Review of the Pathogenesis, Clinical Aspects and Treatment, New England J. Med. **214:** 1236, 1936.
34. Gamble, J. L., and Ross, G. G.: The Factors in the Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1:** 407, 1925.
35. Darrow, D. C.: Changes in Muscle Composition in Alkalosis, J. Clin. Investigation **25:** 324, 1946.
36. Wangensteen, O. H.: Care of the Patient Before and After Operation, New England J. Med. **236:** 121, 1947.
37. Vaughan, H. H., Iob, L. V., and Moyer, C. A.: Postoperative Salt Intolerance, Ann. Surg. **119:** 533, 1944.

Case Reports

MECONIUM PERITONITIS

CHARLES HUGH MAGUIRE, M.D.,* AND WILLIAM RAY MOORE, M.D.,
LOUISVILLE, KY.

PERITONITIS in the newborn infant due to single or multiple perforations of the intestinal tract in utero with an outpouring of meconium into the peritoneal cavity is a relatively uncommon entity; however, it apparently occurs with enough frequency to warrant bringing the condition to the attention of the general practitioner, obstetrician, and pediatrician. It is probably true that some cases of meconium peritonei go unrecognized until surgical intervention is useless and hopeless. We hope to bring out a few pertinent factors that may help induce earlier recognition of the condition so that surgical correction may be carried out before the newborn infant is *in extremis*.

Meconium peritonitis is a sterile chemical peritonitis in contradistinction to bacterial peritonitis of the newborn infant, which does occasionally occur. As brought out by Williams[1] and DeLee,[2] meconium is composed of desquamated epithelial cells, bile pigments and bile salts, and sebaceous material from aspirated amniotic fluid and gastrointestinal juices. Antipartum escape of meconium into the peritoneal cavity will thus result in a purely chemical peritonitis. If, however, perforation of the bowel occurs 36 to 48 hours post partum, then bacterial peritonitis may occur, since contamination of the intestinal tract of the newborn infant occurs a relatively few hours after birth.

It is of interest to note the time of appearance of meconium in the embryo. Mall[3] described meconium in the cecum of a 130 mm. embryo, while others listed the second trimester as the time of appearance of meconium. In some cases, the time of appearance of the meconium might be of some importance in an attempt to determine the approximate time of rupture of the intestine and leakage of meconium into the peritoneal cavity.

ETIOLOGY

There is apparently no single adequate explanation as to the cause of meconium peritonitis. A number of conditions have been listed as etiological factors but no single factor is sufficient to explain all of the reported cases.

Meconium ileus, an entirely different entity, has been repeatedly reported. Adamson and Hild,[4] Dodd,[5] Kornblith and Otani,[6] Bronough and Lattimer[7] reported cases of meconium ileus and/or intestinal obstruction without perforation of the intestinal wall at any point. At the time of autopsy it was found that the meconium was quite firm and almost puttylike in consistency. In many of these cases there was either obstruction of the pancreatic ducts by inspissated

Received for publication, July 28, 1949.
*From the University of Louisville School of Medicine.

meconium or congenital stenosis of the ducts. Regardless of the cause of obstruction of the pancreatic ducts, it is now known that if no pancreatic juices pass into the intestinal tract the meconium will assume this firm, puttylike character.

With this factor in mind, it is easy to visualize a combination of factors that would result in prenatal perforation of the intestinal tract and resultant meconium peritonitis. If there were partial or complete obstruction of the small bowel, secondary to atresia or congenital diaphragms, and partial or complete obstruction of the pancreatic ducts, then a set of circumstances is present which might produce meconium peritonei. Hard, puttylike meconium would be propelled against the partially or completely obstructed segment of intestine by the peristaltic force of the proximal bowel; then, either necrosis of the bowel wall due to constant pressure by the hard meconium, or actual explosion of a blind pouch might occur with resulting meconium peritonitis. On the other hand, with a single, completely obstructed segment low in the ileum, it might seem possible that normal meconium could be thrust against such a barrier over a period of time with enough force so that eventual necrosis of the bowel wall, perforation, and peritonitis would follow; however, there is adequate evidence that with normal meconium and normal structure of the bowel wall proximal to or at the point of partial or complete obstruction, perforation of the bowel wall does not necessarily follow. Davis and Poynter[8] collected 401 cases of congenital atresia or obstruction of the small bowel and colon in which there was no perforation of the proximal segment. The areas of obstruction were as follows: duodenum above ampulla, 59; duodenum below ampulla, 75; jejunum, 60; ileum and cecum, 101; colon, 39; and multiple areas, 67. This group did not include any cases of rectal or rectosigmoid obstruction.

It must be realized that in this remarkable group, collected by Davis and Poynter, in which no perforations had occurred, obstruction had been complete since formation of the lumen of the intestine in the embryo; it must follow that perforation of the bowel wall does not occur unless there is some congenital weakness in the involved portion of small bowel and/or partial or complete obstruction of the pancreatic ducts so that the meconium becomes hard and puttylike.

Lattes[9] and Boikan[10] have felt that antipartum perforation of the ileum has been due to marked hypertrophy of the glands of Lieberkühn so that the apices of the glands reached the serosa of the bowel, together with congenital weakness of the muscle coats of the intestinal wall.

Lattes reported pseudomyxoma peritonei in a case of fatal meconium peritonitis. The mother had begun to have evidence of polyhydramnios at about 8 months and delivered a 3,980 Gm. baby that measured 40 cm. at the umbilicus. It was noted at the time of delivery that the amniotic fluid was stained and slightly foul. The infant died soon after delivery and an autopsy showed perforation of the ileum. Microscopic examination of the wall of the ileum close to the point of perforation revealed marked hypertrophy of the glands of Lieberkühn and thinness of the muscle coats of the intestinal wall. Boikan reported one case of antipartum rupture of the ileum in which there had been perforation

of the ileum 60 cm. proximal to the ileocecal valve. Here again, there was hypertrophy of the glands of Lieberkühn and thinness of the muscle coats of the intestinal wall. There was also a marked increase in the amount of lymphoid tissue in the wall of the ileum at the point of perforation. Boikan included an extensive review of the literature.

Markowitz and Loar[11] reported a case in which there had been multiple pin-point perforations of the jejunum. At the time of autopsy it was found, on microscopic section, that there was a marked overgrowth of lymphoid tissue in the wall of the involved jejunum. It may be a debatable point in this reported case whether the perforations were secondary to the overgrowth of lymphoid tissue or the increase in lymphoid tissue was secondary to the perforations.

Markowitz and Loar also mentioned trauma as a possible cause of meconium peritonitis. Their patient was about 6½ months pregnant when she was accidentally kicked in the abdomen by her 7-year-old son. She had immediate severe pain and almost went into shock. She recovered in about 24 hours. In the following 3 weeks she developed evidence of polyhydramnios, and at about 8 months of gestation she went into labor and was delivered of this child. Death of the infant occurred about 24 hours post partum.

Farr and Brunkow[12] also mention congenital bands, atresia, and volvuli as possible etiological factors.

CASE REPORT

We are reporting a single case of meconium peritonei in which there had been spontaneous rupture of the ileum in utero at a point approximately 15 cm. proximal to the ileocecal valve.

Mrs. E. H., 26 years of age, first pregnancy, had expected the date of confinement to be about Jan. 18, 1948. There had been fairly normal abdominal enlargement during the sixth month of pregnancy. During the early days of the seventh month there had been rather marked enlargement of the abdomen. At about 7 months and 3 weeks she went into labor suddenly and after 20 hours of labor, from a right occipitoanterior position, delivered a 4 pound, 8 ounce male child. The obstetrician (W. R. M.) noticed 3 important factors: first, there was an unusually large amount of amniotic fluid for this size child; second, the amniotic fluid was slightly brown-tinged and had a faintly fetid odor; third, the abdomen of the infant was moderately distended.

The delivery was completed at 3:35 P.M. on Dec. 15, 1947. During the night, the infant vomited parts of his formula and on the following morning it was found that there was moderate distention present, and percussion elicited a flat note throughout the abdomen. A left indirect inguinal hernia was present. X-ray examination revealed 2 important findings: first, there was free air in the peritoneal cavity (Fig. 1); second, small flecks of calcium and several larger strips of calcium were visualized scattered throughout the peritoneal cavity (Fig. 2).

An operation was carried out approximately twenty-eight hours post partum. Following the induction of very light ether anesthesia, the abdomen was opened through an incision splitting the right rectus muscle. Upon incising the peritoneum, a pseudocyst wall was encountered, which measured approximately 6 mm. in thickness. This pseudocyst wall was apparently made up of inspissated meconium and fibrin and, upon opening, was found to contain approximately 600 c.c. of thin meconium. Further exploration revealed the liver, stomach, and spleen to be displaced upward and enveloped by a similar covering. The entire intestinal tract was displaced posteriorly and lay in both iliac fossae, the individual loops of

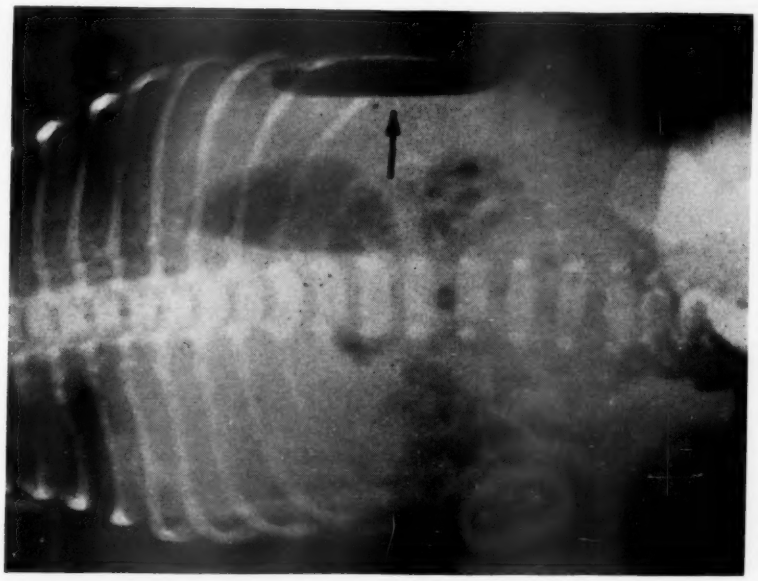


Fig. 1.—Right lateral decubitus x-ray film showing intraperitoneal air.

Fig. 2.—Upright abdominal film showing strips of calcium.

bowel being matted together and covered with this inspissated meconium and fibrin. In the right lower quadrant of the cystlike cavity there were 2 open ends of ileum, about 5 mm. apart, protruding into the cystlike cavity and appearing much like a double-barrelled enterostomy. This area was gradually dissected free and the point of spontaneous rupture and complete division was found to be approximately 15 cm. proximal to the ileocecal valve. Anastomosis of the 2 ends of ileum was carried out using No. 000000 catgut sutures in the inner tier and 000000 silk as the outer tier of sutures. The abdomen was then closed in layers after partial removal of the fibrinomeconial layer of pseudocyst wall.

The infant had a fairly stormy course for 3 days and then apparently began to improve. On the seventh and eighth postoperative days he took all of his formula, and he had begun to pass small meconial stools. On the evening of the eighth day, he began to lose ground rather rapidly and died on the ninth postoperative day. Unfortunately, an autopsy was not obtained.

It was of interest at the time of operation to find that the mucosa of the distal segment of ileum had not been stained by meconium and was partially filled with a cheesy material resembling vernix caseosa. Apparently true meconium had never been in this distal segment. It would have been of interest to have obtained an autopsy in order to determine the patency of the pancreatic ducts. It is true that the meconium in the pseudocyst was quite liquid, but chemical irritation of the peritoneum would have caused an outpouring of a transudate of sufficient quantity to dilute the meconium had it been firm and puttylike.

The exact mechanism of the production of meconium peritonei is not clear in this case; however, apparently there was present a given set of circumstances which produced actual and complete explosion of the involved segment of ileum.

Comment.—We have presented a single case of meconium peritonei and have attempted to correlate some of the theories in regard to the etiology of the condition. Apparently, one of the most constant findings, as brought out by Neuhauser,[13] is the roentgenologic one of flecks of calcium scattered throughout the peritoneal cavity. Strangely enough, there is no definite time relationship between the outpouring of meconium into the peritoneal cavity and the formation of these calcium flecks and strips. Some authors believe that such calcium can be deposited within as short a time as 48 hours.

The early diagnosis of meconium peritonei is not difficult if several important factors are kept in mind:

1. Discoloration of the amniotic fluid and the presence of a fetid odor should put the obstetrician on his guard.

2. Abdominal distention in a newborn infant is a finding that cannot be ignored. Antipartum perforation of a gastric or duodenal ulcer and polycystic kidneys are other conditions that will have to be considered in a differential diagnosis.

3. Vomiting and the absence of meconial stools in a newborn infant indicates that the intestinal tract is obstructed or is not in continuity.

4. The roentgenologic findings are almost pathognomonic. Flecks and streaks of calcium throughout the peritoneal cavity are entirely characteristic. Free air in the peritoneal cavity is sufficient evidence that perforation of the intestinal tract has occurred and that surgical intervention is obligatory.

5. It is possibly true that meconium peritonei may be one factor responsible for the production of polyhydramnios and premature labor. This was seen in our case and in the cases reported by Lattes and by Markowitz and Loar.

SUMMARY

1. A case of meconium peritonitis is presented with positive physical, x-ray, and operative findings.

2. Etiological factors are discussed.

3. Emphasis is placed on findings which may lead to an early post-partum diagnosis and prompt surgical correction.

REFERENCES

1. Williams, J. W.: Obstetrics, New York, 1926, D. Appleton & Company.
2. DeLee, J. B.: The Principles and Practice of Obstetrics, ed. 6, Philadelphia, 1933, W. B. Saunders Company.
3. Mall: quoted from Boikan.[10]
4. Adamson, E. W., and Hild, Jack R.: J. A. M. A. **112**: 2275, 1939.
5. Dodd, K.: J. Pediat. **9**: 486, 1936.
6. Kornblith, B. A., and Otani, S.: Am. J. Path. **5**: 249, 1929.
7. Bronough, Wayne, and Lattimer, R. D.: Am. J. Dis. Child. **60**: 1371, 1940.
8. Davis, D. L., and Poynter, C. M. W.: Surg., Gynec. & Obst. **34**: 35, 1922.
9. Lattes, Raffaele: Am. J. Obst. & Gynec. **46**: 149, 1943.
10. Boikan, W. S.: Arch. Path. **9**: 1164, 1930.
11. Markowitz, B., and Loar, Ralph: Am. J. Obst. & Gynec. **27**: 733, 1934.
12. Farr, R. E., and Brunkow, C. W.: Arch. Surg. **11**: 417, 1925.
13. Neuhauser, E. B. D.: Am. J. Roentgenol. **51**: 421, 1944.

BOECK'S SARCOID OF THE PANCREAS

JOHN F. CURRAN, JR., M.D.,* AND JOHN F. CURRAN, SR., M.D.,†
WORCESTER, MASS.

(From the Worcester City Hospital)

BOECK'S sarcoid as a generalized disease is readily recognized from its clinical and laboratory findings. However, when the disease is restricted to a single organ, the manifestations are then masked and the diagnosis is not readily reached. Certain syndromes of this disease entity have been classified according to the organs involved, which has facilitated the clinical evaluation. However, a rather extensive survey of the literature failed to reveal case reports of sarcoidosis restricted to the confines of the pancreas. The case to be presented was one which presented surgical manifestations and tested our diagnostic acuity.

HISTORY

The following is a brief summary of the literature on Boeck's sarcoid from the historical standpoint. Besnier, in 1889, first described an entity with lesions involving the ears, nose, and fingers, which he named lupus pernio. Later, in 1899, Boeck[1] described the lesions of the mucous membranes, skin, and lymph nodes as sarcoid. Heerfordt, in 1909, classified uveoparotid fever, which only recently was recognized to be a form of sarcoidosis.[2, 3, 4] Not until 1914 did Schaumann appreciate that Boeck and Besnier indefinitely described various manifestations of the same generalized disease which had a specificity for the lymphatic and hemopoietic systems.[4, 14]

INCIDENCE

No age group has been spared of the disease, although the majority of cases have fallen within the second to the fourth decades. To date the Negro population has had a slightly higher incidence.

PATHOLOGY

The pathologic lesion is a microscopic collection of epithelioid cells due to the proliferation of histiocytes. Occasionally a cell of the Langhans' giant type is found with acid-stain inclusion bodies. It is generally believed that necrosis and caseation do not occur and a reticulum persists. Tubercle bacilli are not isolated, and lymphocytes, though they may be present peripherally, are not conspicuous. The lesions exhibit a tendency toward slow healing by fibrosis and hyalinization.[5, 11, 16]

Various groups of well-known syndromes have been described because of a combination of organ involvement such as uveoparotid fever, Mikulicz syndromes, and osteitis multiples cystoides, but apparently no organ has immunity to attack from sarcoidosis. The lymph nodes, in particular the cervical, axillary, mediastinal, and inguinal, are the most commonly effected. Pulmonic involve-

Received for publication, Nov. 5, 1949.
*Senior Surgical Resident, Worcester City Hospital.
†Senior Surgeon, East Surgical Service, Worcester City Hospital.

ment is frequent and has been classified according to the x-ray impression. Approximately 35 per cent of the patients exhibit skin manifestations, and the incidence of bone involvement is 25 per cent. Splenomegaly occurs in about 25 per cent of the cases, with hepatomegaly in 15 per cent. The eye becomes involved in 50 per cent, though it is not always restricted to the uveal tract. The parotid gland and mucous membranes are affected to an incidence of 10 per cent, and the systemic manifestations may involve with lesser frequency the myocardium, breasts, spinal cord, brain, thyroid, small intestine, pituitary gland, and gastrointestinal tract, including the testes and epididymis.[5, 8, 9]

CLINICAL COURSE

The course may be one of an acute episode with remission into a subacute or chronic phase. Regression may be interrupted by an exacerbation with new generalized manifestations. Spontaneous healing may occur by fibrosis. To date, 25 per cent of the cases reported have been fatal, and the complication factor has been tuberculosis in 75 per cent.[10, 16] It appears that an individual afflicted with Boeck's disease is more readily subjected to pulmonary tuberculosis in its more malignant forms.

LABORATORY DIAGNOSIS

The diagnosis is generally suspected on the clinical findings and x-ray interpretation, although the microscopic biopsy confirmation is necessary. Certain laboratory data, such as a negative or a weak tuberculin test,[12, 13] are suggestive and aid in establishing the diagnosis. Other indications are: an absolute monocytosis and/or an eosinophilia, an elevated blood sedimentation rate, hyperproteinemia with hyperglobulinemia, and occasionally a hypercalcemia with an elevated alkaline phosphatase.[6, 7, 11, 15]

This rather bizarre manifestation of sarcoidosis with localization to the pancreas exhibits some of the typical diagnostic criteria, though the clinical diagnosis is by no means obvious.

CASE REPORT

M. B., a 48-year-old woman, was admitted to the Worcester City Hospital complaining of easy fatigability of six months' duration.

Illness at Time of Admission.—The patient had been hospitalized one year previously for acute alcoholism. For six months following her discharge she experienced excellent health, after which she noticed easy fatigability which was progressive in character. The only associated symptoms were frequency of urination (six times during the day) and nocturia (twice at night). Her appetite was only fair, with no specific food intolerance. In the following four months there was a weight loss of fifteen pounds. Six weeks prior to admission she developed a girdle type of dull pain across the upper abdomen and back. This pain was constantly present from its onset and sometimes described as being "burning" in nature. Associated with it was a chilly sensation which occurred once daily and lasted but a few seconds. Two weeks prior to admission the pain became crampy and localized to the epigastrium without radiation and appeared at irregular intervals. There was no definite relationship to meals. Frequently it kept her awake at night and was somewhat relieved by the use of a hot water bag or by taking warm water, soda bicarbonate, or milk by mouth. The patient had become chronically constipated, for which strong cathartics were constantly used. The stools, however, were described as

being normal in appearance. Two days before admission the patient became nauseated and vomited a brown material. She continued to vomit four to five times daily until the sixth day in the hospital. The material was never noticed to be coffee-ground.

Past History.—The patient had a past history of an appendectomy, two cesarean sections, and a hysterectomy. There was one admission for bromide poisoning five years ago. Phlebitis with residual postural edema of two years' duration was present.

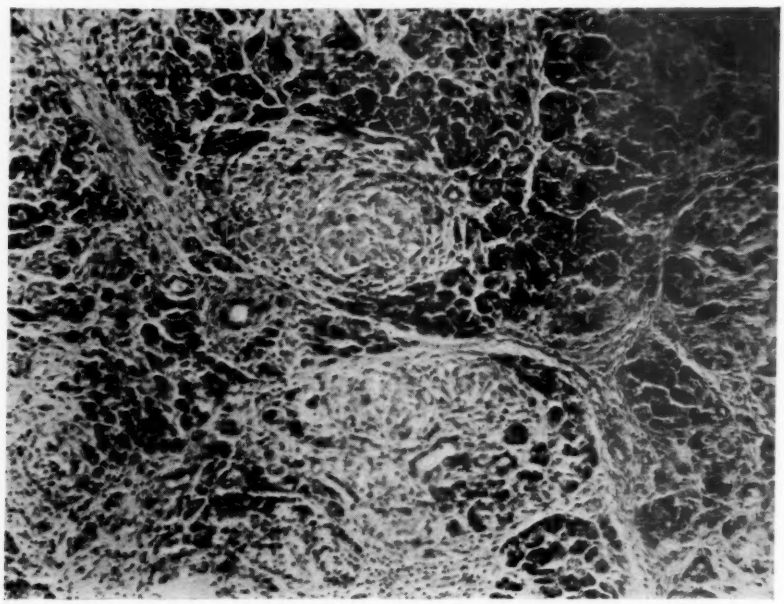


Fig. 1.

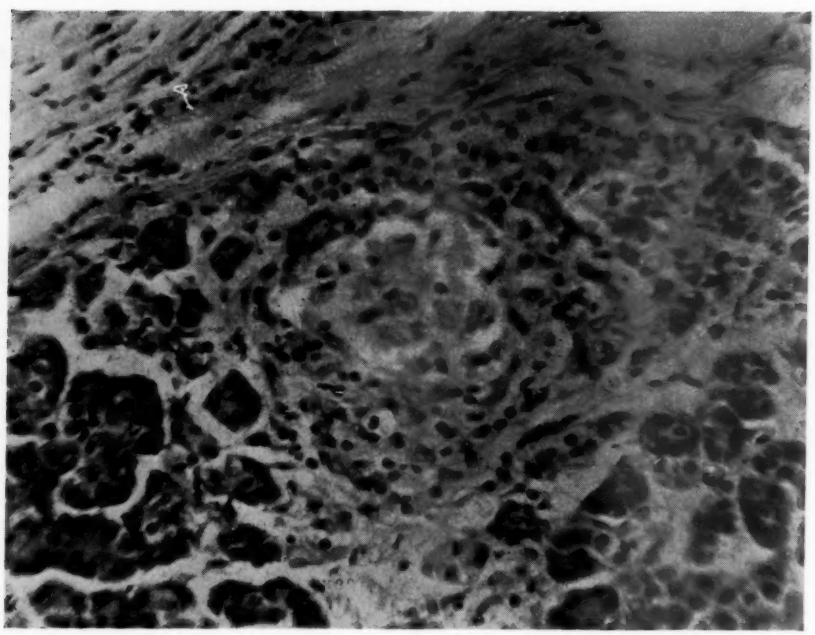


Fig. 2.

Figs. 1 and 2.—The pancreas is partly replaced by tubercles made up of epithelioid cells and an occasional foreign body giant cell. A few lymphocytes are scattered around the tubercles. Caseation necrosis is absent.

Physical Examination.—Physical examination revealed a 48-year-old woman, well nourished, and in no acute distress. Temperature was 99.4° F., pulse 80, respirations 20. The only positive physical findings were a soft abdomen with slight gaseous distention. There was superficial skin tenderness in the right upper quadrant, but no deep tenderness in this region. No masses could be palpated. The extremities exhibited marked saphenous varicosities with edema of the right pretibial region. Neurological examination revealed only hyperactive reflexes and absent abdominal reflexes.

Laboratory Data.—The red blood count was 4.6 million; hemoglobin, 91 per cent; and white blood count, 5,600, with a differential of 60 polymorphonuclears, 24 leucocytes, 10 monocytes, and 6 eosinophils. Folin blood sugar was 91; nonprotein nitrogen, 33; blood cholesterol, 154 mg.; and serum amylase, 16 units. The Hinton and Kahn tests were negative. The urine was negative except for a slight trace of albumin and an occasional white blood cell and red blood cell. The total protein was 6.1, albumin 3.9, and globulin 2.1. Stools were consistently positive for fat and meat fibers.

Clinical Course.—The patient was admitted on the medical service and vomiting was combated with sedatives, atropine, and a bland regime. A chest film and bone survey were reported as negative. A Graham-Cole series was done and only a poorly functioning gall bladder was visualized. A fluoroscopy and a gastrointestinal series were negative and an intravenous pyelogram showed good excretion with some rigidity of the right pelvis and kinking at the right ureteropelvic junction. On the twentieth hospital day the patient was explored and all organs appeared normal with the exception of the pancreas, which was twice normal in thickness, and firm and nodular throughout. A biopsy from the head of the pancreas was microscopically Boeck's sarcoid.

The convalescence was uneventful and the patient was placed on pancreatic enzymes by mouth and the appropriate diet. Eighteen months after operation the patient was asymptomatic, had gained weight, and was working daily. To date no other manifestations of Boeck's sarcoid have been detected.

DISCUSSION

This patient, who exhibited the clinical and laboratory findings consistent with chronic pancreatitis, had certain consistent findings with sarcoidosis such as the monocytosis and a high total protein with an elevated globulin. The tuberculin test was negative, which is also contributory. The exact diagnosis was made only by microscopic study of the pancreatic biopsy. The patient has been given only supportive therapy and substitution pancreatic enzymes with apparently good effect. Nearly two years postoperatively she is maintaining a good state of nutrition and is entirely asymptomatic. As yet the islet cells have not been involved sufficiently to produce a diabetic syndrome and no other clinical manifestations of sarcoidosis have occurred.

SUMMARY AND CONCLUSIONS

This is the presentation, after eighteen months' study, of a rather unusual case of Boeck's sarcoid which has involved only the pancreas. The diagnosis was confirmed by biopsy and the patient has been asymptomatic on pancreatic enzyme substitution therapy. The prognosis may be one of complete remission of the disease or in the future one of the more common syndromes of sarcoidosis may appear.

Acknowledgment.—We wish to express our gratitude to Raymond H. Goodale, Pathologist, Worcester City Hospital.

REFERENCES

1. Boeck, C.: Multiple Benign Sarcoid of Skin, J. Cutan. & Genito-Urin. Dis. **17**: 543, 1899.
2. Michelson, H. E.: Sarcoidosis; a Review and an Appraisal, J. A. M. A. **136**: 1034, 1948.
3. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**: 223, 1937.
4. Longcope, W. T.: Sarcoidosis or Besnier-Boeck-Schaumann Disease, J. A. M. A. **117**: 1321, 1936.
5. Thomas, C. C.: Sarcoidosis, Arch. Dermat. & Syph. **47**: 58-73, 1943.
6. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid With Particular Reference to Protein, Calcium, and Phosphate Values, J. Clin. Investigation **18**: 687-693, 1939.
7. Danboet, N.: On Kveim's Reaction in Boeck's Disease, Acta. med. Scandinav. **114**: 143, 1943.
8. Harrell, G. T.: Generalized Sarcoidosis of Boeck's. A Clinical Review of Eleven Cases With Studies of the Blood and the Etiologic Factors, Arch. Int. Med. **65**: 1003, 1940.
9. Hunter, F. T.: Hutchinson-Boeck's Disease (Generalized Sarcoidosis), New England J. Med. **214**: 346, 1936.
10. Salvesen, H. A.: The Sarcoid of Boeck: Disease of Importance to Internal Medicine, Acta med. Scandinav. **86**: 127, 1935.
11. Goeckerman, W. H.: Sarcoids and Related Lesions: Report of Seventeen Cases; Review of Recent Literature, Arch. Dermat. & Syph. **18**: 237, 1928.
12. Curtis, A. C., Taylor, A., and Grekin, R. H.: Sarcoidosis I. Results of Treatment With Varying Amounts of Calciferol and Dehydrotachysterol, J. Invest. Dermat. **9**: 131, 1947.
13. Pinner, M.: Noncaseating Tuberculosis; an Analysis of the Literature, Am. Rev. Tuberc. **37**: 690-728, 1938.
14. Hannesson, H.: Besnier-Boeck's Disease, Brit. J. Tuberc. **35**: 88-113, 1941.
15. Nickerson, D. A.: Boeck's Sarcoid; Report of 6 Cases in Which Autopsies Were Made, Arch. Path. **24**: 19-29, 1937.
16. Curtis, Arthur C., and Grekin, R. H.: Sarcoidosis III; a Review, M. Clin. North America **33**: 31-54, 1949.

BRONCHIAL TUMORS: THORACOBRONCHOTOMY

A. Lincoln Brown, M.D., San Francisco, Calif.

(From the Surgical Service, Thoracic Surgery Section, Mount Zion Hospital)

BRONCHOSCOPIC enucleation of intrabronchial tumors is a now accepted mode of attack upon those lesions assumed to be benign. This method always poses the question of whether or not the lesion has been completely eradicated from the bronchial wall. No knowledge is obtained, by this procedure, of the tumor's possible extrabronchial extension.

Exploratory thoracotomy has, with advances in thoracic surgery and anesthesia, become a highly safe and useful procedure. Thoracotomy allows one to ascertain whether or not an extrabronchial extension of an intrabronchial lesion exists, what damage may have been done to the lung distal to the intrabronchial lesion, and, combined with bronchotomy, it permits the complete excision of benign lesions, plastic repair of the bronchus, and conservation of the maximum functioning of pulmonary parenchyma. Bronchotomy, particularly in the larger bronchi where a longitudinal incision is made in the posterior membranous portion of the bronchus, is simple and heals readily (Fig. 1, *A* and *B*). The term thoracobronchotomy is used simply to designate the operative procedures of thoracotomy and transthoracic bronchotomy.

Resections of portions of the bronchus and plastic operations upon bronchi are highly successful.[1, 2] Not only is complete eradication more feasible by this direct attack, but the difficulties, uncertainties, and dangers of endoscopic operations (such as hemorrhage, and incomplete removal) are avoided. Furthermore, areas out of the range of vision or operability by endoscopic means may be successfully visualized, and appropriate measures simply instituted under direct vision once exploratory thoracotomy has been undertaken.

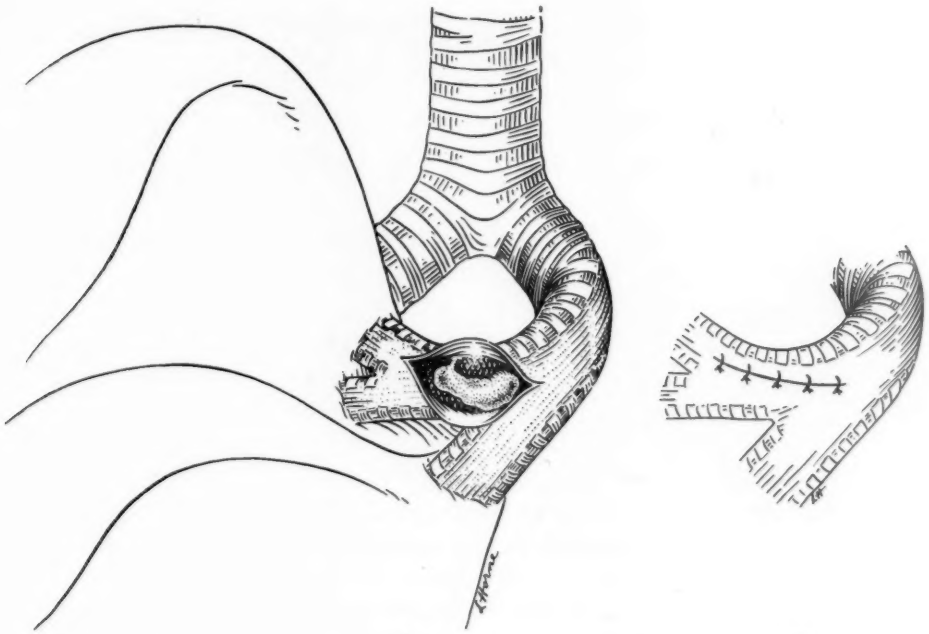
Thoracobronchotomy is especially applicable in bronchial tumors, bronchostenosis, and bronchial injuries. Many intrabronchial tumors (that is, adenomas) may have extrabronchial extensions. Definitive surgery, no more or less extensive than absolutely indicated by direct examination, suggests that thoracobronchotomy must be considered as the probable method of choice in many intrabronchial tumors and other bronchial lesions.

The removal of a bronchial tumor by thoracobronchotomy is illustrated by the following case report. The tumor in this instance proved to be a very rare benign granular-cell myoblastoma of the bronchus. Apparently this is the third such tumor to be recorded.[3, 4] Its complete removal was effected with the preservation of all pulmonary parenchyma.

Received for publication, Nov. 9, 1949.

CASE HISTORY

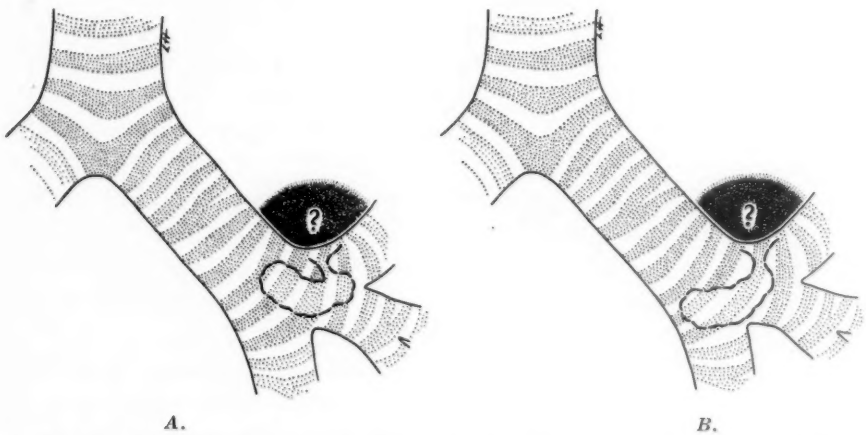
D. L., a 48-year-old man, was referred Dec. 6, 1948, with a presumptive diagnosis of bronchial obstruction of the left lower lobe. The patient gave a five-month history of cough, frothy sputum, no hemoptysis, and dyspnea, which was particularly severe when he lay on the right side. At bronchoscopy Dec. 7, 1948, a lobulated tumor presented out of the orifice of the left upper lobe bronchus. The lobulated mass filled approximately two-thirds



A. *B.*

Fig. 1.—A, Diagrammatic representation of left lung displaced toward the right bronchotomy through the membranous posterior portion of the left upper lobe bronchus. Facile accessibility of the intrabronchial tumor by this maneuver is obvious.

B, Interrupted silk suture of membranous portion of bronchus. Sutures do not include epithelial layer.



A. *B.*

Fig. 2.—*A*, Diagrammatic representation showing position of pedunculated tumor with patient lying on left side. The dotted area with the ? mark represents possible extrabronchial tumor extension whose presence or absence can be determined only by thoracotomy.

B, Position assumed by this pedunculated tumor when patient attempted to lie on the right side. Almost complete main-stem bronchial occlusion took place, with resulting severe respiratory embarrassment.

of the left main-stem bronchus and had the characteristics of an adenoma, though somewhat less vascular than usual. The base of the tumor could not be visualized. Biopsy was done. The microscopic sections were inconclusive except that they were reported as showing no evidence of malignancy. Exploratory thoracotomy was decided upon.

Preoperative Diagnosis.—The preoperative diagnosis was a benign bronchial tumor.

Operation.—Thoracobronchotomy was done with excision of bronchial tumor.

Anesthesia.—Intratracheal sodium pentothal, cyclopropane, nitrous oxide, ether was used.

Procedure.—The thoracic cavity was opened through the fifth interspace. There was no free fluid in the pleural cavity. The lung lobes were normally expanded. No masses or unusual lymph nodes were felt in the hilar region. The left main-stem bronchus was located and freed from surrounding vessels and lung tissue by means of blunt dissection until the left upper lobe main bronchus was reached. This was dissected free up to its first division. No peribronchial or extrabronchial extension of the growth which was known to be present within the bronchus was found. It was decided, therefore, to perform a bronchotomy and

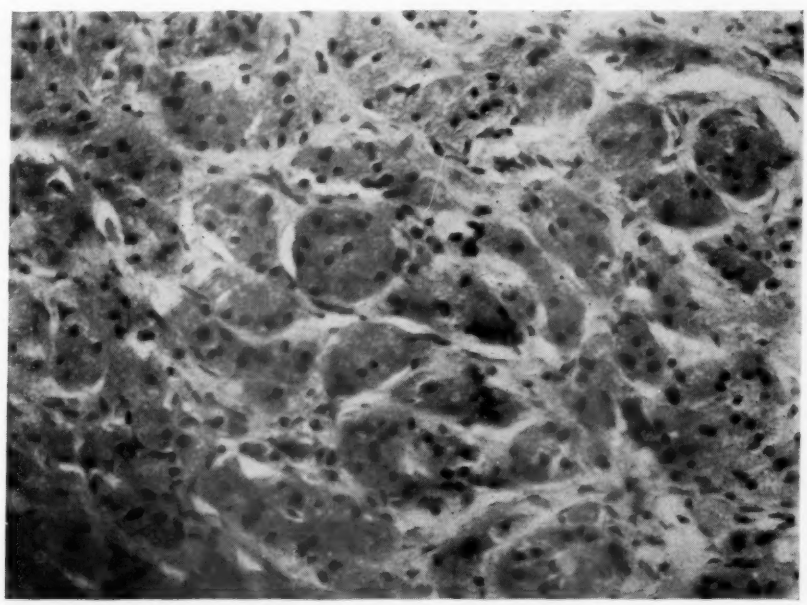


Fig. 3.—Photomicrograph (×100) of section of tumor removed at bronchotomy showing typical granular-cell myoblastoma of the bronchus.

excision of the tumor through this opening. Two umbilical tapes were placed underneath the left upper lobe main bronchus in order to steady it, and a longitudinal incision was carried through the bronchial wall, thus exposing a relatively firm, encapsulated, slightly friable, nodular tumor which was adherent to the bronchial mucosa by means of a rather wide base, and which almost occluded the entire bronchus at the opening into the left main-stem bronchus.

The tumor was removed using sharp dissection. Its base was curetted. There was very little bleeding, and suction was used in order to cleanse the neighboring bronchi. Hemostasis was accomplished by pressure.

The longitudinal incision in the bronchus was closed using medium silk end-on mattress sutures. The chest cavity was then filled with saline solution and it was ascertained that the closure was airtight. Closure was effected without drainage.

Postoperative Diagnosis.—The postoperative diagnosis was probable bronchial adenofibroma in the left upper lobe main bronchus.

Pathologic Report.—The tumor tissue was reported* as benign granular-cell myoblastoma of the bronchus.

Postoperative Course.—The postoperative course was entirely uneventful. The patient was discharged from the hospital on the tenth postoperative day. He has remained well and a check bronchoscopy nine months after removal showed no evidence of any recurrence.

CONCLUSIONS

Thoracobronchotomy in selected cases is a valuable adjunct to the thoracic surgeon's armamentarium.

REFERENCES

1. Crafoord, Clarence, discussion following Rabin, C. B., and Neuhof, Harold: Adenoma of the Bronchus, J. Thoracic Surg. **18**: 149-163, 1949.
2. Gebauer, Paul: Plastic Reconstruction of Tuberculous Bronchostenosis With Dermal Grafts, J. Thoracic Surg. **19**: 604-628, 1950.
3. Kraus, A. R., Melnick, P. J., and Weinberg, J. A.: Myoblastoma of the Bronchus, J. Thoracic Surg. **17**: 382-389, 1948.
4. Kramer, R.: Myoblastoma of Bronchus, Ann. Otol., Rhin. & Laryng. **48**: 1083-1086, 1939.

*By Dr. Gerson Biskind.

CARCINOMA OF THE BREAST—WHY THE UPPER OUTER QUADRANT?

W. RALPH DEATON, JR., M.D., AND H. H. BRADSHAW, M.D.,
WINSTON-SALEM, N. C.

(From the Department of Surgery, Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital)

THE majority of carcinomas of the breast arise in the upper outer quadrant (Fitts,[1] 58 per cent; Finney,[2] 56 per cent; Deaton,[3] 58.9 per cent). It seems likely that the high incidence of the disease in this location exists because aberrant breast tissue is frequently located at the upper outer quadrant, contiguous to the breast, and may be the site of carcinoma that is diagnosed simply as carcinoma of the breast. Several theories[4-7] have been advanced to explain the high incidence of carcinoma of the upper outer quadrant, but the part that aberrant breast tissue may play has not been mentioned previously, as far as can be ascertained from a search of the literature. The following case definitely illustrates carcinoma arising in aberrant breast tissue.

Mrs. L. C. Z. (NCBH No. 1796), a 41-year-old white female, was first admitted to this hospital on Dec. 1, 1931. She complained of having had "pain and lumps" in the left breast for several years, with each symptom increasing steadily in severity for the previous five years following the last of four pregnancies. The breast had been incised and drained for abscesses during three of the pregnancies. On December 2, under ether anesthesia, a complete simple mastectomy was performed. The gross and microscopic diagnosis was chronic cystic mastitis. Recovery was uncomplicated. Sometime during 1936 she noticed the presence of a painless firm nodule, "about the size of a dime," at the anterior pectoral fold, just superior to the lateral margin of the mastectomy scar. The nodule did not increase in size until early 1941, when she noted that it was slightly larger than before. On June 26, 1941, she was seen as an outpatient and a diagnosis of excessive cicatrix made. Under local procaine infiltration anesthesia, the nodule, with a surrounding area of normal skin and subcutaneous tissue, was removed. Microscopic sections revealed scirrhous carcinoma of the breast, grade 3. There was no involvement of the skin, to suggest a cutaneous recurrence, nor was there any lymphoid tissue present to suggest development of a long-delayed metastasis. She was treated with radium irradiation, and did well until 1947 when lung metastases developed. She died on June 16, 1948, of liver, lung, and pleura metastases. This was seventeen years after the simple mastectomy and seven years after being treated for carcinoma of aberrant breast tissue. Had she not previously had a simple mastectomy, this cancer would surely have been classified as originating in the upper outer quadrant.

Carcinoma arising in aberrant breast tissue is not unusual,[8] and the site of origin is easily recognizable when the aberrant tissue and the normal tissue are not contiguous. However, the most frequent location of aberrant tissue is at the upper outer quadrant of the breast,[9, 10] although it may occur anywhere along the mammary ridge, which runs in a sinusoid curve from the axilla to the groin.[10] Surveys have shown that aberrant tissue occurs in from 1 to 7 per cent of the people, and is more frequent on the left,[11] as is carcinoma of the breast.[1, 2] It appears reasonable to assume that carcinoma of aberrant breast tissue adjacent to the normal breast may be diagnosed as carcinoma of the breast itself. It is impossible to differentiate, microscopically, aberrant breast tissue from normally

Received for publication, Nov. 25, 1949.

located breast tissue.[12] As an explanation for the frequent presence of carcinoma in the aberrant breast tissue, stagnation, with its resulting irritation, is believed to be the chief predisposing factor. (Adair[7] showed experimentally in mice that stasis is one of the main factors in the etiology of breast cancer.) Logically, there should be more stagnation in aberrant tissue than in any part of the normal breast, due to the frequent absence of external openings of the drainage ducts supplying the aberrant tissue.[11] The aberrant tissue does not drain into the normal breast as the two are independently formed from separate anlages of ectodermal tissue.[11, 13, 14] Even if a nipple is present over the accessory gland, the drainage system may be incomplete, leading to stagnation.[15] Moreover, there may be an as yet unrecognized factor present that acts to incite malignant changes in any aberrant tissue; for example, there is a high incidence of cancer in aberrant thyroid tissue.[16]

In summary, a case is presented in support of the theory that the high incidence of breast carcinoma in the upper outer quadrant of the breast is due in part to carcinoma that arises in aberrant breast tissue in that area. Incidently, this case should serve as a warning to surgeons to insure removal of all breast tissue, both normally and abnormally situated, when performing simple mastectomy.

REFERENCES

1. Fitts, W. T., Jr., and Donald, J. G.: The Diagnosis of Lesions of the Breast, SURGERY **25**: 424, 1949.
2. Finney, G. G., Merkel, W. C., and Miller, D. B.: Carcinoma of the Breast, Ann. Surg. **125**: 673, 1947
3. Deaton, W. R., Jr., Postlethwait, R. W., and Bradshaw, H. H.: Carcinoma of the Breast, North Carolina M. J. **10**: 484, 1949.
4. Nicholson, W. P., Jr.: Prophylaxis of Mammary Cancer, South. Surgeon **12**: 325, 1946.
5. Nicholson, W. P., Jr.: Carcinoma of the Breast: Its Treatment and Prevention, South. Surgeon **13**: 354, 1947.
6. Nicholson, W. P., Jr., and Grady, E. D.: Carcinoma of the Breast, Ann. Surg. **127**: 992, 1948.
7. Adair, F. E., and Bagg, H. J.: Breast Stasis as the Cause of Mammary Cancer, Internat. Clinics **4**: 19, 1925.
8. Cole, W. H., and Rossiter, L. J.: in Lewis' Practice of Surgery, volume 5, chapter 6, Hagerstown, Md., W. F. Prior Company, Inc.
9. Iwai: Cited by Speert, H.: Supernumerary Mammae, With Special Reference to the Rhesus Monkey, Quart. Rev. Biol. **17**: 59, 1942.
10. Hertzler, A. E.: Surgical Pathology of the Mammary Gland, Philadelphia, 1933, J. B. Lippincott Company, pp. 36.
11. Schaeffer, J. P.: Morris' Human Anatomy, ed. 10, Philadelphia, 1942, The Blakiston Company, pp. 71.
12. Lide, T. N.: Personal communication.
13. Robinson, A.: Cunningham's Text-Book of Anatomy, ed. 5, New York, 1923, William Wood & Company, pp. 1320.
14. Davis, G. G.: Applied Anatomy, revised by G. P. Muller, Philadelphia, 1926, J. B. Lippincott Company, pp. 184.
15. Geschickter, C. F.: Diseases of the Breast, ed. 2, Philadelphia, 1947, J. B. Lippincott Company, pp. 139.
16. Lahey, F. H.: Cancer of the Thyroid, Am. J. Roentgenol. **46**: 469, 1941.

Surgical Technique

TECHNIQUE OF PNEUMONECTOMY

ALTON OCHSNER, M.D., NEW ORLEANS, LA.

(From the Department of Surgery, Tulane University, and The Ochsner Clinic)

PNEUMONECTOMY may be performed for a number of conditions, such as neoplastic disease, particularly carcinoma, extensive cystic disease with secondary infection, extensive suppurative disease involving the entire lung, or a drowned lung secondary to obstruction of one of the major bronchi by an inflammatory process such as tuberculosis. There is no unanimity of opinion concerning the approach that is to be used in performing a pneumonectomy, but most thoracic surgeons prefer a posterolateral approach for the performance of a pneumonectomy or lobectomy. Whereas a lobectomy is best performed through a posterolateral incision which permits dissection of the hilum from many sides, it is my conviction that pneumonectomy, particularly for neoplastic disease, unless there is evidence of involvement of the chest wall, is best performed through an anterior incision. This incision, popularized by Rienhoff, is preferable in patients with neoplastic disease for several reasons. Carcinoma of the lung occurs with few exceptions in older persons, those in the fifth, sixth, and seventh decades, who because of their age are more likely to have cardiovascular disorders than younger individuals. Respiratory and cardiovascular functions are less altered when the patient is in the supine position than in the lateral decubitus position, particularly when, as is necessary in performing a pneumonectomy through a posterolateral incision, the uninvolved lung is dependent and compressed by the weight of the body. An additional reason why the anterior approach is preferable to the posterolateral one in performing a pneumonectomy is that the distance from the skin to the mediastinum, in which the entire dissection is done, is shorter through an anterior approach than through a posterolateral approach. Another advantage in having the patient in the supine position is that there is less danger of spillage of secretions from the involved lung into the uninvolved lung than when the patient is in the lateral decubitus because in the latter, gravity facilitates the passage of secretions into the dependent normal lung. Probably one of the reasons why the anterior approach has not become more popular is the difficulty in securing adequate length of the pulmonary vessels through an anterior incision. However, as will be described later, this difficulty can be overcome readily by "walking" the ligature into the mediastinum, thus obviating this criticism of the anterior approach.

The patient is placed in a supine position on the operating table but in order to facilitate the efforts of the assistants, the side to be operated upon is slightly elevated above the surface of the table by means of sandbags placed under the

Received for publication, Feb. 9, 1950.

shoulder and the hip on the affected side. A similar position can be obtained with the patient flat on the table by tilting the table so that the side to be operated upon is elevated.

The incision is made in the third intercostal space, extending from the mid-portion of the sternum to the midaxillary line. The skin, subcutaneous fat, and pectoralis major and minor muscles are divided. After exposing the intercostal muscles in the third intercostal space throughout the entire length of the incision and exposure of the lateral border of the sternum, the intercostal muscles.

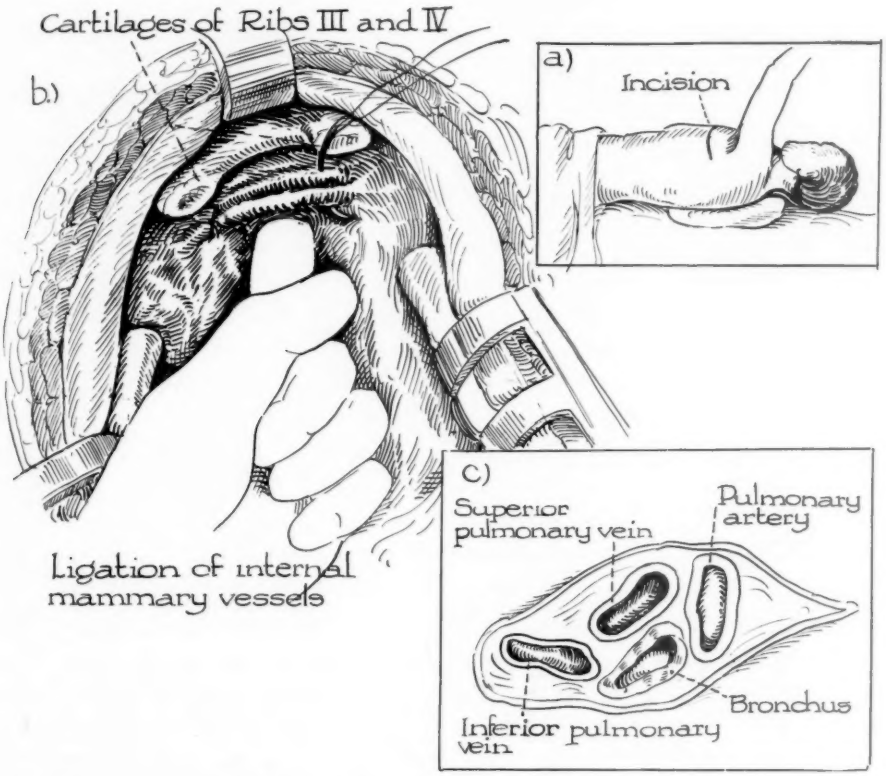


Fig. 1.—Incision used for right pneumonectomy. With the shoulder and hip slightly elevated by means of sandbags placed under them, incision is made in the third intercostal space, extending from the mid-portion of the sternum to the midaxillary line. *b*, The pleural cavity has been opened in the mid-portion of the wound, and the incision extended medially to the internal mammary vessels. The third and fourth costal cartilages have been removed, and transfixion sutures are being placed around the internal mammary vessel. *c*, Relationship of the hilar structures on the right side. The pulmonary artery lies superiorly and anteriorly. The superior pulmonary vein is inferior to the pulmonary artery and anterior to the bronchus. The inferior pulmonary vein is most inferior of the hilar structures, whereas the bronchus is the most posterior.

in about the mid-portion of the incision, are incised immediately above the fourth rib. The incision is extended laterally to the edge of the wound and is extended medially to within approximately 3 cm. of the sternal edge or until the internal mammary vessels are visible. The third and fourth costal cartilages are divided as near the sternum as possible, and the medial portion of the respective costal cartilages are removed flush with the sternum by means of a large rongeur. The internal mammary vessels are exposed and crochet cotton No. 20 transfixion sutures are placed around them in the upper and lower parts of the wound re-

spectively. After ligation of the internal mammary artery and vein, they are divided in the mid-portion of the incision and the ends of the respective vessels are clamped and ligated (Figs. 1 and 2).

After opening the pleura throughout the entire length of the incision, rapid examination of the pleural cavity is made to determine the presence or absence of adhesions. If there are no adhesions between the lung and the anterior chest wall, the wound is opened further by separating the third and fourth ribs with a suitable retractor such as the one described by Finochietto. The ribs should

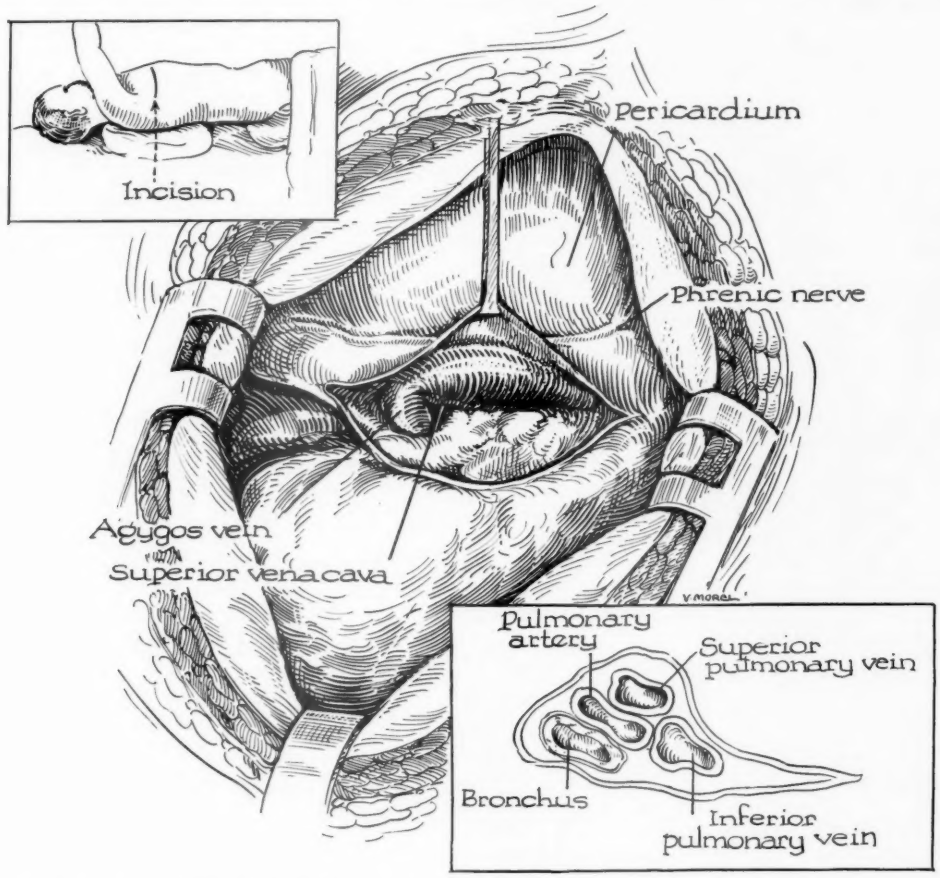


Fig. 2.—Insert shows position of the patient on the table and the incision used for a right pneumonectomy. After opening the pleural cavity in a manner as described in Fig. 1, incision is made in the mediastinal pleura posterior to the phrenic nerve, which is extended above and below around the hilus. The vena azygos major is isolated in order that it may be ligated. The lower insert shows the relationship of the hilar structures on the right side. The bronchus is the most superior of all the structures and also the most posterior. Immediately anterior to it and somewhat inferior is the pulmonary artery and the superior pulmonary vein lies anterior and inferior to the pulmonary artery, slightly overriding it. The inferior pulmonary vein is the most inferior of all the structures.

be separated slowly in order not to break them and to permit adequate relaxation of the chest wall. After sufficient retraction of the adjacent ribs has been secured, careful exploration of the hemithorax is done to determine the presence or absence of adhesions and the extent of extrapulmonary involvement, particularly in the mediastinum. Even in cases in which there is apparently extensive involvement of the mediastinum, resection is frequently possible and

frequently only after considerable dissection of the mediastinal structures has been accomplished can one determine whether the lesion is resectable or not. Unless dissection of the hilar vessels, because of mediastinal involvement, cannot be accomplished, or unless the heart or aorta are involved, resection is usually possible.

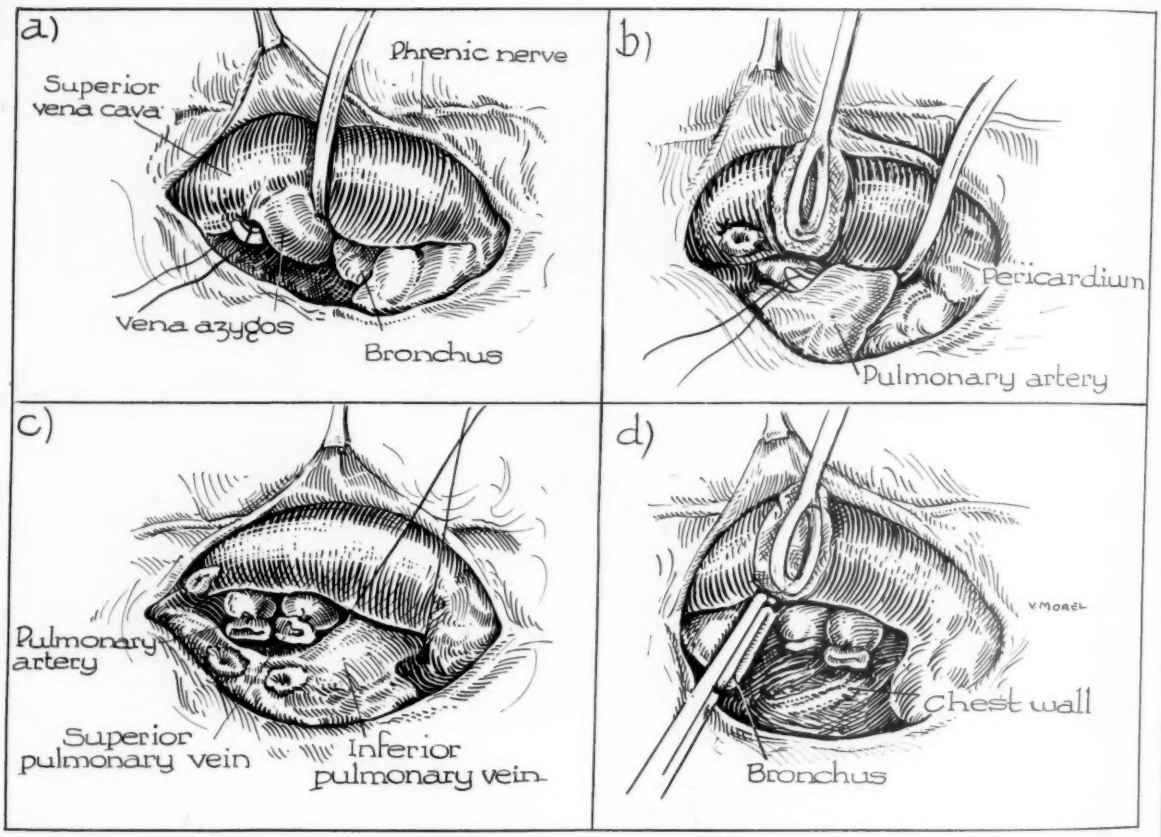


Fig. 3.—The vena azygos major is dissected free from the surrounding areolar tissue, and ligatures are placed around it to permit ligation. This is desirable to prevent injury to the vena azygos major in the dissection of the bronchus. *b*, The superior vena cava is mobilized medially in order to secure adequate exposure of the hilar vessels. The vena cava is retracted medially by means of a sponge held in a sponge forceps. The pulmonary artery has been isolated by a combination of digital and "dissector" dissection and a ligature is being placed around the vessel. *c*, The pulmonary artery and the superior pulmonary vein having been ligated and doubly transfixed medially and ligated and transfixed laterally are divided distally in order to leave a long proximal segment. The inferior pulmonary vein has been isolated and a ligature placed around it. *d*, Three hilar vessels, the pulmonary artery, the superior pulmonary vein, and the inferior pulmonary vein, have been ligated and divided. The bronchus has been isolated, doubly clamped, and divided.

A longitudinal incision is made in the mediastinal pleura posterior to the phrenic nerve and extending around the root of the lung. On the right side (Fig. 2) the vena azygos major as it empties into the superior vena cava is isolated and freed from its surrounding structures. Because of the danger of injuring this vessel when dissecting the bronchus, it is desirable to doubly ligate and divide it. By means of a suitable instrument such as Semb ligature carrier, crochet No. 20 cotton ligatures are placed around the vena azygos major, which is ligated with sufficient length between the ligatures to permit safe division.

In addition to ligation medially and laterally, transfixion cotton sutures are introduced and tied. The vena azygos is divided (Fig. 3, *a*).

Although there may be some variation in the order of dissection, generally the first hilar structure to be dissected is the pulmonary artery. On the right side, the superior vena cava overlies the pulmonary vessels, and for this reason it is necessary to mobilize the cava medially in order to expose them adequately. Mobilization of the cava is secured by a combination of blunt and sharp dissection, the blunt dissection being done by means of small pledgets of gauze held in long curved forceps (dissectors). Retraction medially of the vena cava is secured by a sponge in a sponge holder held by an assistant (Fig. 3, *b*). Separation of the pulmonary artery from the superior pulmonary vein inferiorly and from the bronchus posteriorly and inferiorly is best secured by digital dissection.

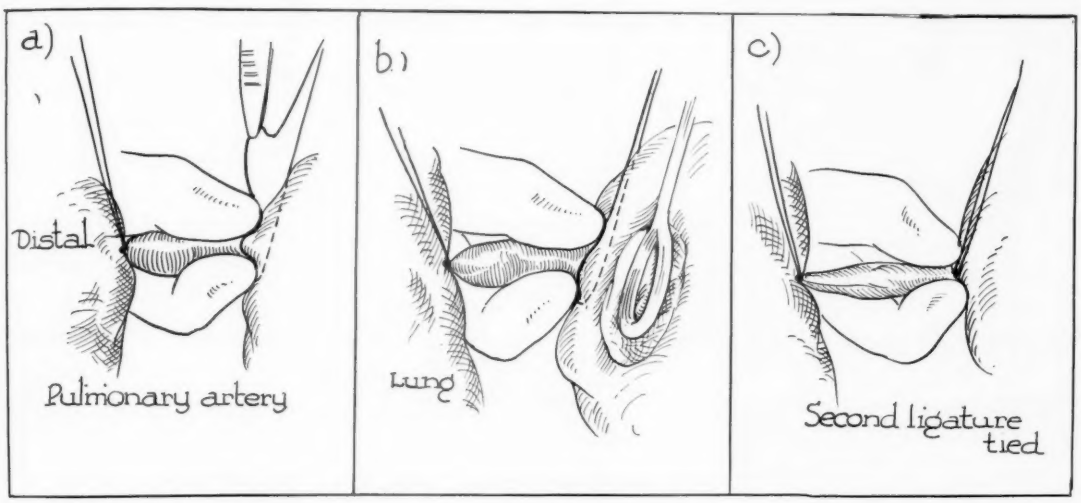


Fig. 4.—Diagram showing the technique of ligation of the pulmonary vessels. *a*, The distal ligature has been tied, and the proximal ligature is being "walked" into the mediastinum. This is accomplished by keeping the proximal ligature taut and by means of a long tissue forceps advancing the ligature first on one side and then on the other, the surgeon maintaining the position of the advanced ligature by means of the index finger posteriorly and the thumb anteriorly. *c*, The proximal ligature is tied by the assistant while the surgeon maintains the ligature in its medial position by means of the index finger and thumb. Not until the first knot of the ligature has been tightened and seated, which, because of the large size of the vessel, requires several seconds, are the surgeon's thumb and finger removed.

Occasionally a combination of digital and "dissector" dissection is desirable. After the superior pulmonary artery has been completely isolated, a curved ligature carrier (Semb) is introduced around it and crochet cotton No. 20 ligatures are drawn around the artery. The lateral ligature is tied immediately adjacent to the lung, thus securing the distal portion of the pulmonary artery immediately before it enters the lung. In order to secure a long segment of the vessel to permit division of the vessel with sufficient length so that slippage of the ligature will not occur, the technique of "walking" the ligature into the mediastinum is used (Fig. 4). The assistant retracts the mediastinum medially and holds taut the proximal ligature. The operator places the index finger around the artery posteriorly and by means of a long tissue forceps advances the ligature proximally into the mediastinum, taking a step on one side of the

artery and then on another, in this way "walking" it into the mediastinum. During this maneuver the surgeon's index finger posteriorly and the thumb anteriorly advance medially, maintaining the ligature in a medial position where it is held while the assistant ties it. If the ligature were not "walked" into the mediastinum and held in position by the operator's hand, the tension required to tighten the ligature would dislocate the ligature laterally and an insufficient length of the artery would be secured. Not until the knot has been tightened and the ligature seated, which requires several seconds of time because of the large size of the vessel, are the surgeon's thumb and index finger removed. The

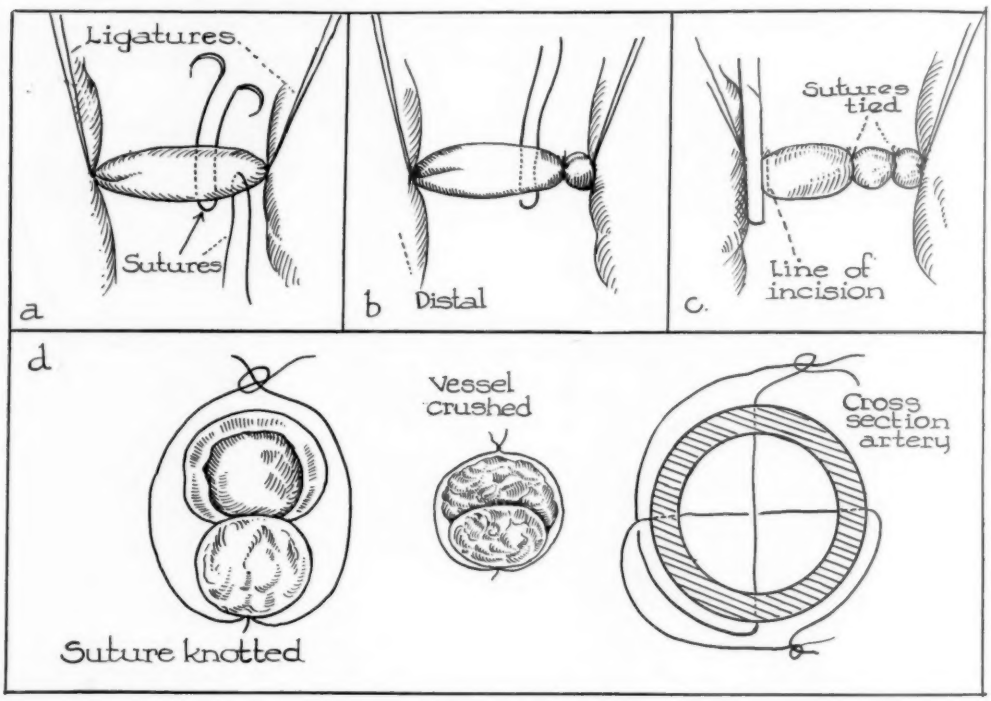


Fig. 5.—Diagrammatic drawing showing the technique of double transfixion proximally in order to secure four quadrants of the vessel. The proximal and distal ligatures have been tied, isolating a considerable segment of the vessel. Two transfixion sutures are introduced proximally, one passing from the superior to the posterior surfaces and another from the anterior to the posterior surfaces. After introduction of the individual suture, one-half of the vessel is compressed by tying the ligature, following which one end of the ligature is drawn around the vessel, and the ligature again tied. In this way four quadrants of the vessel are secured by the two transfixion ligatures. As shown in *c*, a large Ochsner clamp is placed immediately adjacent to the lung on the distal portion of the vessel and the vessel is divided immediately adjacent to the clamp, leaving a long segment of vessel on the cardiac side.

second and third knots on the ligature are then completed. In this way a long segment of vessel can be obtained relatively easily. Because of the large size of the vessel, simple ligation of the pulmonary artery is not sufficient but should be supplemented by double transfixion ligation, placing the ligatures in such a way that four quadrants of the vessel are secured. This is accomplished by inserting one suture, a No. 20 crochet cotton threaded on a French eye needle, through the vessel from the superior to the inferior surfaces and another suture from the anterior to the posterior surfaces. Each of these sutures is tied, first on the one side and then, after drawing one of the sutures around the vessel by

means of a Semb ligature carrier, on the opposite side (Fig. 5, *d*). By using the two transfixion sutures introduced in this way, the four quadrants of the diameter of the vessel are secured. Finally, a transfixion suture is placed distally immediately adjacent to the lung. Although this may seem unnecessary, because the lung is to be removed, it prevents back bleeding if the distal ligature should happen to become displaced or loosened. A large Ochsner forceps is placed on the artery immediately adjacent to the lung and the artery is divided immediately medial to the clamp (Fig. 5, *c*). In this way, a long segment of the vessel distal to the proximal ligatures is secured, the ligatures having been inserted in such a way that slippage is almost impossible.

Following ligation and division of the pulmonary artery, the superior pulmonary vein is next treated in a manner similar to that used for the pulmonary artery. After division of the superior pulmonary vein, the inferior pulmonary ligament is exposed by retracting the lower lobe laterally and superiorly. Because the inferior pulmonary ligament is usually vascularized, it is doubly clamped, divided, and ligated. Careful dissection is extended upward to the inferior pulmonary vein, which is treated as were the pulmonary artery and superior pulmonary vein.

The pulmonary hilum is now freed with the exception of the posterior reflection of the pleura, the mediastinal lymph nodes, and the bronchus. The bronchus is carefully dissected out up to the carina, removing the lymph nodes from around it. After isolating the bronchus by means of the finger and separating it from the surrounding tissue, it is compressed and the anesthetist determines whether or not the patient is able to breathe. This is of importance in order to prevent possible injury to the trachea in a patient with extensive nodal involvement in which the trachea may be mistaken for the main stem bronchus. If the patient is able to breathe satisfactorily following compression of the bronchus, two right-angled clamps are applied to the bronchus, one immediately distal to the carina and the other ½ cm. distally. The trachea is divided between the two clamps, and the posterior reflection of the pleura from the lung onto the mediastinum is incised. The lung is thus freed and can be removed. Frequently, small vessels extending to the mediastinal lymph nodes are present which should be clamped, divided, and ligated.

Following removal of the lung, the bronchus is closed by introducing interrupted sutures of No. 20 crochet cotton proximal to the clamp. The sutures at the two ends are tied proximal to the clamp immediately after their introduction (Fig. 6, *a*). The other sutures are not tied until the clamp is removed, but are then tied snugly but not tightly. It is important not to tie these sutures too tightly because of the possibility of cutting through the bronchus. In this way the bronchial lumen is closed adequately and there is no leakage (Fig. 6, *b*).

The bronchial stump is covered with mediastinal pleura by suturing the anterior or superior edge of the mediastinal pleura to the posterior or inferior edge or by mobilizing adjacent portions of the mediastinal pleura to cover the stump (Fig. 7, *a*). Although this is not absolutely essential, it is desirable because it favors a localized collection of fibrin and subsequent organization with

the production of a fibrous tissue cap over the bronchus which will prevent the bronchial stump from blowing out if the sutures should subsequently slough out.

The phrenic nerve is crushed in order to permit elevation of the diaphragm and to decrease the size of the cavity. No drainage is instituted because it is desirable that the hemithorax fill with exudate which later will become a fibrinous

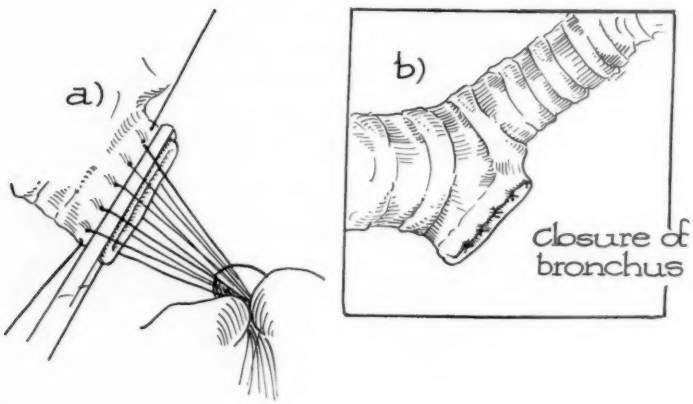


Fig. 6.—Diagrammatic drawing showing the technique of closure of the bronchus. The bronchus has been divided between clamps. Sutures are introduced proximal to the clamp, the two ends being tied before removal of the clamp. These serve as gut sutures. The other sutures are left in place and held taut until the clamp is removed, following which they are tied snugly but not too tightly.

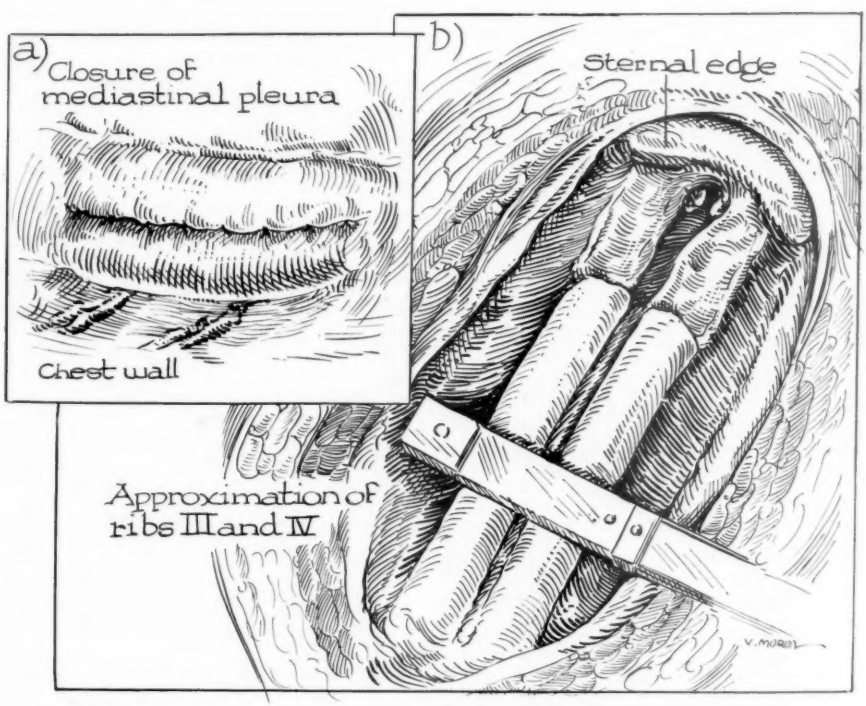


Fig. 7.—*a*, The bronchial stump has been covered by suturing the edges of the anterior and posterior mediastinal flap. If this is not possible, the mediastinal pleura should be mobilized to cover the bronchus. This permits collection of serous fluid in a pocket around the bronchial stump. Later, fibrin will be deposited, which subsequently will become organized, producing a fibrous cap over the bronchus. *b*, The adjacent third and fourth ribs are approximated by means of an approximator and the chest closed.

and subsequently a fibrous network. The thoracic wound is closed by approximating the adjacent ribs with a rib approximator (Fig. 7, *b*). Pericostal sutures of crochet cotton are placed around the adjacent ribs, and tied. Careful approximation of the pectoralis major and minor muscles and the superficial fascia is secured with interrupted quilting cotton sutures. A catheter is placed temporarily in the wound anteriorly during the wound closure and is removed after the patient is returned to the supine position. Because the patient is tilted away from the side being operated upon, there is a slight displacement of the mediastinum toward the opposite side. After the operation has been completed,

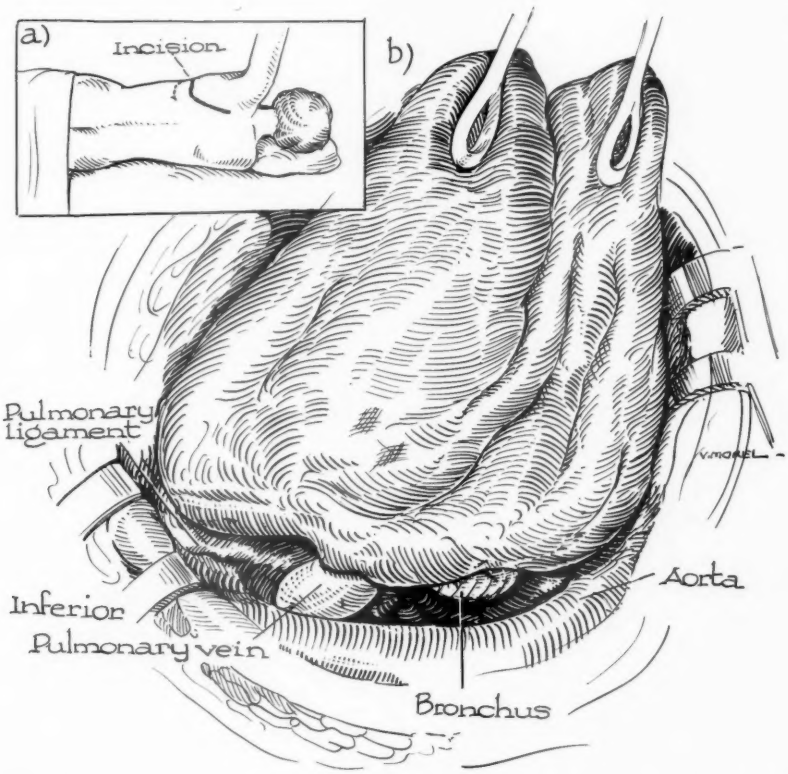


Fig. 8.—Incision used in the posterolateral approach. With the patient in the lateral decubitus, the incision begins paravertebrally in the fifth intercostal space and extends around the angle of the scapula to continue anteriorly in the fifth intercostal space. The fifth and sixth ribs are divided paravertebrally and the intercostal muscles incised throughout the length of the incision. The lung can be mobilized on all sides. The most inferior structure, as shown in *b*, is the inferior pulmonary vein, whereas the bronchus is the most posterior.

the patient is brought back into the supine position or the sandbags are removed from beneath the shoulder and hip which permits the mediastinum to shift back in its normal position. Trapped air within the pleural cavity can then escape through the catheter, following which the catheter is removed and the skin suture closed. A compression bandage is applied to the wound using elastoplast.

In cases in which there is a likelihood of involvement of the chest wall and in which it may be desirable to resect major portions of the chest wall or diaphragm because of extension to these structures, the posterolateral approach is preferred. It is probably preferable also in cases in which there are extensive

adhesions between the lung and the parietes. Although undesirable generally from the standpoint of the welfare of the patient and also more difficult because of the greater distance from the chest wall to the mediastinum, this is performed with the patient in the lateral decubitus, lying on the sound side. The incision beginning paravertebrally in the fifth intercostal space extends downward, curves around the angle of the scapula to curve superiorly again, and anteriorly in the fifth intercostal space (Fig. 8). After division of the skin, subcutaneous fascia, trapezius, and latissimus dorsi muscles, the ribs are counted from above in order to identify definitely the fifth intercostal space. The fifth and sixth ribs are divided in their paravertebral portions, exposure of this portion of the rib being secured by retraction of the erecta spina mass medially. A short segment of the rib is removed in order to prevent overriding of the rib end following closure of the wound. The incision is made in the fifth intercostal space, dividing the intercostal muscles at the upper border of the sixth rib. The pleura is opened throughout the extent of the wound. Subsequent performance of the pneumonectomy differs in no way from that in which the anterior approach is used.

Editorial

THE ethic of surgical practice is a delicately balanced system played upon by two equally essential, but at least occasionally conflicting, influences, the one entirely unselfish, the other selfish. It is primarily assumed that one performs an operation only for the good of the patient, and yet there is a second reason, the reward to the surgeon. He must feed and house and clothe his family. He must maintain a level of living commensurate with his position in his community. In short, if he is to continue to do the good of which he is capable, he must earn enough to satisfy these requirements. For any surgeon a moral problem may at times be present. It is asking more than human perfection to assume that a surgeon's judgment may not be influenced unconsciously by pressing financial need.

A wise and experienced gynecologist has pointed out that fees have progressively become smaller step by step with an increasing "professional feeling of service toward the patient." This development over the centuries represents a forward movement toward better conditions of practice. Whatever may be said of improvements needed today, it is well to recognize that doctors by their own efforts have advanced steadily toward the goal of the finest service to the patient in all aspects, economic as well as medical and psychologic.

In commenting upon the moral conflict between surgical indications and fee, one must remember that it affects only the conscientious practitioner of surgery. The so-called surgeon who practices primarily for the fee, who advises operation without adequate study, who removes a normal organ without indications, who makes an emergency out of almost every case, has no problem of morals, nor has the occasional general practitioner who undertakes procedures for which he is not trained or who does an incomplete operation for malignant disease so that at least some of the surgical fee will stay at home. These men do not belong in the honorable company of surgeons. The conscientious, careful surgeon who studies his patients thoroughly, thinks through the problem presented, and then is troubled to find a temptation that might taint his judgment, faces the moral issue. If he is the man we assume him to be, we need not be worried about his performance of unnecessary surgery.

The other class of surgeon constitutes a menace to the unsuspecting patient and an equally real threat to the good name of surgery. In these days of inquiry into the workings of the medical profession, these men give us all a bad name. To the outsider, one who wields a scalpel is a surgeon; a finer estimate of quality may not be possible. If some surgeons perform unnecessary operations for a fee, then all surgeons can be suspect for the same malfeasance. One of the urgent tasks for surgical leaders today is to face the problem. The fringes of the skirts of surgery must be lifted from the mire. Already this problem is the subject of preliminary study by authoritative surgical groups.

At the present time, the matter has become increasingly urgent for two reasons, the one general and the other specific. The first is the widespread impression that the ancient moral code of the medical profession has softened in some of its fibers. The growing selfishness that has resulted in refusal to answer patient calls at night is a case in point, as is the recently publicized habit of certain physicians to accept rebates from manufacturers and salesmen. A noble profession is taking on some of the ethics of the market place. If these breakdowns of medical ethics are indeed indicative of a trend, then surgery is seriously threatened.

The second reason is less subtle. The great brake upon unnecessary operations by unscrupulous or incompetent operators has been in the past the fear of fatality. The extraordinary developments of surgery in the last ten years have almost removed this brake. The modern methods of protecting the patient by adequate preoperative preparation, properly chosen and skillfully administered anesthesia, continuous support on the operating table, and alert postoperative care are available to the unjust as well as to the just. It is easy to remove a normal gall-bladder or a normal uterus if only one in 200 will succumb. How different it was in the days when one in ten or even one in five could be expected to die. Now the operator can be reasonably certain that his reputation for saving his patients is secure. How simple it has been made for him! This fact alone makes it urgent at all cost to salvage the good name of surgery.

—*Edwin P. Lehman, M.D.*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

EXPERIMENTAL RESECTION OF THE TRACHEA

DONALD J. FERGUSON, M.D.,* JOHN J. WILD, M.D., AND
OWEN H. WANGENSTEEN, M.D., MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Medical School)

FOR about seventy years the trachea has been a subject of occasional experimental interest to surgeons; owing to the fact that its diseases are uncommon, however, it remains rather unfamiliar ground. Nevertheless, in most large hospitals, patients may be found who would benefit from radical excision of tracheal lesions if the operation were safe and well understood. It will be worth while, therefore, to summarize the progress thus far made, and to explore further some aspects of tracheal resection in animals.

The first experimental anastomoses of the trachea were probably those described in 1881 by Gluck and Zeller. In an attempt to prevent aspiration pneumonia following operations on the larynx, they divided, the trachea of dogs between the third and fourth rings and brought the 2 ends out on opposite sides of the neck. In some of the dogs laryngectomy was performed successfully four days later. In others, after a longer time, the 2 ends of the trachea were dissected free and sutured together. The animals recovered.

Kuester, whose case was reported by Colley, successfully resected and anastomosed a human trachea for stricture in 1884. Surgeons of that era had to deal with tracheal strictures fairly often; diphtheria was common, and throat-cutting was in vogue as a method of attempting suicide.

Inspired by Kuester's case, Colley (1895) described a series of tracheal resections in dogs. In 5 instances, 3 rings were removed from the cervical trachea, and the ends were sutured together with silk or catgut. Three of the dogs developed strictures and in efforts to circumvent these, oblique incisions were made through 5 rings, 5 rings apart, and an elliptical anastomosis was performed. The anterior flap of tracheal wall thus formed came loose, even when stiffened with silver wire, and obstructed the trachea. Finally, the anterior and posterior halves of the trachea were divided at different levels, and connected by vertical incisions. The suture lines on the anterior and posterior walls were thus separated, and though scars formed they did not produce obstruction.

Subsequent resections of the trachea in human beings were reported by Eiselsberg (1896), Föderl (1896), and Hacker (1902), and within a few years

The researches presented here were supported by the following funds for cancer research: The United States Public Health Service, Grant No. RG1028; Malignant Disease Research Fund, University of Minnesota; and The Graduate School, University of Minnesota.

Received for publication, Feb. 28, 1950.

*Damon Runyon Clinical Research Fellow.

there were a large number of cases (Nowakowski, 1909). Circular incisions were generally employed, and catgut was the favored suture material. Segments from 2 to 4 cm. in length were removed.

Nowakowski determined in human cadavers that it was feasible to remove 3 to 4 cm. of the trachea and suture it end-to-end, with the neck in neutral position. Five centimeters could be removed in ⅔ of the experiments. Less could be excised from those with long necks, where the annular ligaments were already stretched.

Where the diseased segment of trachea was too long to resect, parts of the circumference were removed (Bruns, 1898). Many ingenious methods for covering large tracheal defects have been devised. König (1896) described the use of a skin flap containing an attached piece of thyroid cartilage; other methods utilized skin flaps with part of the sternum or clavicle attached (König, 1897); skin flaps stiffened temporarily with needles (Trnka, 1900); silver gauze (Grosse, 1901); and free transplants of costal cartilage (Mangoldt, cited by Niehues, 1903). Usually two pedicled skin flaps were made, so that an epithelial surface was presented toward the tracheal lumen. Free skin grafts have also been placed successfully into defects in the tracheal mucosa following excision of scar tissue.[10, 19]

In many instances, both in human beings and in dogs, free fascial grafts have been used with some success to cover small tracheal defects involving usually not over 1 cm. of the circumference.[6, 7, 15, 18, 20, 23, 28, 33] The graft apparently does not survive, but is replaced by fibrous tissue and is covered after 2 or 3 weeks with respiratory epithelium. The use of fibrin film to cover small tracheal defects has resulted in stricture formation.[6]

The use of rigid tubing to bridge defects in the trachea and primary bronchi has been described recently. Daniel (1948) used tubes made of glass, stainless steel, or Vitallium; the material apparently was unimportant. The tubes were flanged and were held in place by encircling ligatures. Of twenty-one animals in which a segment of thoracic trachea was replaced by a tube, 15 survived. In those sacrificed from 3 weeks to 6 months after operation, regenerating islands of cartilage were present in the connective tissue surrounding the tubes. At 6 months, epithelial regeneration was still incomplete. In a group of 8 dogs, the right lung, lower trachea, and part of the left bronchus were excised and replaced by a Vitallium or glass tube. Of 2 dogs which survived, 1 developed pneumonia at 6 months. The tube came loose in the other dog and was removed after 8 months; the dog was sacrificed at 14 months and was found to have newly formed cartilaginous rings, ½ the normal diameter of the trachea, in the area where the tube had been.

Clagett and associates (1948) used Polythene tubes, flanged at each end and in the middle, to perform a quick anastomosis of the cervical and thoracic trachea in dogs. Most of the dogs did well, but some died when the tubes came loose or collapsed; 1 developed collapse of the trachea when the tube was removed after 9.5 months. It was found that as much as ¼ of the trachea

could be resected and the ends be brought together over the tube. An attempt was made to remove a tumor of the thoracic trachea in a human being with the use of this method. The lower trachea below the tumor was too friable to hold the tube; a pneumonectomy was performed and the polythene tube was fastened into the trachea and the remaining primary bronchus. The upper lobe bronchus was plugged by the tube, resulting in pneumonia and death 6 days after the operation.

Longmire (1948) reported the use of a Lucite tube in repairing a tracheal defect in a patient. After 4.5 months the patient was well and there was firm tissue around the tube.

Maisel and Dingwall (1950) divided the cervical trachea of dogs between rings and anastomosed it with a running silk mattress suture. Segments up to 2.5 cm. were removed. Granulation tissue was observed forming a small bridge over the anastomosis at one week. A stricture developed in one of the 12 dogs used.

Carter and Strieder (1950) reported successful autografts of segments of bronchus from resected pulmonary lobes. Homografts of trachea were also made, and functioned well for a time but were later absorbed, with development of stenosis.

It is evident from this review that important surgical problems remain unsettled. The method of anastomosis should be reliable in the presence of tension and friable tissue, and should not result in stricture formation. Means should be found of determining in a given case how much trachea can be excised, with anastomosis. A satisfactory reconstruction should be developed for defects too large to permit end-to-end anastomosis.

EXPERIMENTS AND RESULTS

Experiments were performed on dogs, generally of large size. The trachea of the dog is about twice as long as that of a human being, though of similar diameter. Twenty excised tracheas from dogs weighing 9 to 27 kg. contained 32 to 47 rings and measured 15.0 to 21.7 cm. in length in the relaxed state. With a pull of 1,000 Gm. they stretched 14 to 45 per cent, to lengths of 20.0 to 30.0 cm. The transverse diameter in the middle ⅓ varied from 12 to 24 cm. in length.[26] It can be stretched 17 to 35 per cent in length. Transverse diameters varied from 16 to 25 mm. in ten specimens examined.

The cartilaginous rings of the canine trachea are thin and flared out at the ends, where they normally overlap. Rings in human beings are rectangular and fairly thick at the ends, and do not overlap.

The left bronchus of the dog usually contains only 3 complete rings, and is about 1 cm. in length. The right main bronchus has, as a rule, only 1 complete ring and is very short. In human beings the left bronchus contains 9 to 12 rings and is 4.1 to 4.7 cm. long; the right has 6 to 8 rings and is 2.5 to 3.4 cm. long.[26] The bronchi in both species are a little larger in diameter on the right, where they are about ¾ the size of the lower trachea.

The position of the head and neck determines the amount of stretch of the trachea. In all the operations to be described, the dogs rested supine on a flat table; whenever measurements were to be made, the body of the mandible was held parellel to the table surface. As soon as the trachea was exposed anteriorly, the length to be resected was marked out and measured in situ without freeing it up. Tension required to bring the ends of the divided trachea together was measured, using a pair of forceps hinged at the center and fastened to a rigid bar by a pivot on 1 handle. A cord attached to the other handle passed over a pulley at the far end of the bar and was attached to a large rubber balloon (Fig. 1). The distance from the hooked tips of the forceps to its hinge was equal to the distance from the hinge to the attached cord. The tips of the forceps were hooked into loops of thread on the 2 ends of the trachea, and an

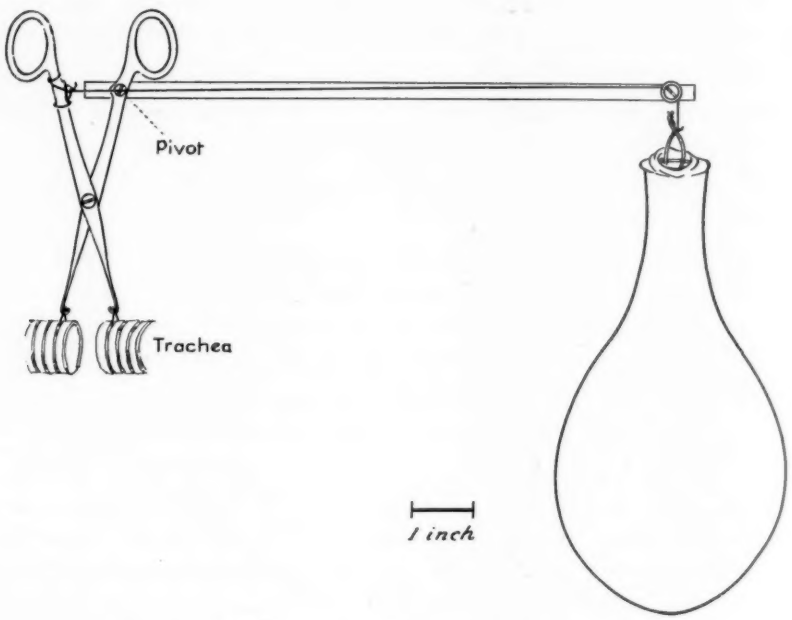


Fig. 1.—Apparatus used to measure tension on the tracheal anastomosis.

amount of water was added to the balloon just sufficient to maintain apposition of the cut surfaces during the inspiratory tug. The amount of water in cubic centimeters plus the weight of the balloon in grams equalled the grams of tension at the site of anastomosis. Friction was neglected and measurements were read only to the nearest 5 Gm. The figures given are for the trachea as a whole; the tension per centimeter would be roughly ⅙ as much. The initial tension was measured when the trachea was first divided, and the final tension after a segment had been resected.

In all operations the usual sterile technique was followed. Penicillin, 5,000 units in 5 c.c. of saline solution, was instilled in the wound just before closure.

Altogether, 92 operations were performed upon 59 dogs. Most of the dogs had been, or were subsequently, used for other unrelated experiments.

A Method of Tracheal and Tracheobronchial Anastomosis.—There are several ways of performing anastomosis of the trachea, and under favorable conditions any of them may be successful. Certain difficulties should be anticipated, however, including strong tension on the anastomosis, friability of the tissues, leakage of air, stricture formation, and discrepancy in diameter of the 2 ends to be sutured. In the experiments to be described, the method of anastomosis which best met these obstacles is the following. Division of the trachea (or bronchus) is begun by incising a cartilaginous ring from 1 end to the other, down to the mucosa, leaving ⅓ to ½ the ring on the end to be sutured. The part of the ring to be removed is then freed up from the underlying mucosa to the next annular ligament, where the mucosa is divided evenly all around the

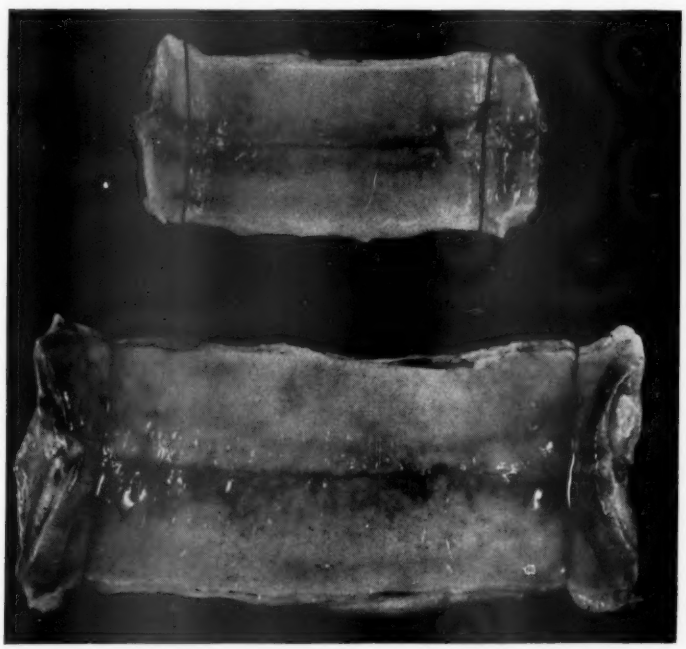


Fig. 2.—Tracheal anastomoses, inner surface; resected on the eighth postoperative day. Interrupted silk. Dogs weighed 30 and 9 kg.

trachea, leaving a small cuff, the edge of which retracts to within a millimeter or 2 of the divided ring (Fig. 10, *c*). The section is completed by dividing the posterior membrane. The other end of the segment to be removed is similarly divided. Anastomosis is begun by placing 3 or 4 sutures through the posterior membrane, not including the mucosa. These are so placed as to adjust any difference in diameter of the 2 ends, so that the more rigid cartilaginous rings will fit evenly all around. Sutures are then placed every 3 mm. around the 2 segments of ring, outside the mucosa. When these sutures are tied the mucosal edges are approximated, and the sutures should not be visible from the lumen (Fig. 2).

When anastomoses of this type were made with 0000 silk in 8 excised human and 15 canine tracheas, the tensile strength was always more than 17 kg.

Similar strength was obtained by suturing around 1 intact ring at each end. Division through the annular ligament and anastomosis with mattress sutures through this ligament gave a tensile strength of 9 to 12 kg. in the same specimens. These figures apply to the whole anastomosis; the tensile strength per centimeter would be approximately ⅙ as much. During the healing period some decrease in strength occurs—a few measurements indicated a loss of about 30 per cent on the fourth to sixth day—but there is evidently a large margin of safety.

Measurements were also made of the amount of intraluminal air pressure these anastomoses would stand before leaking. A manometer was tied into one end of the trachea and a source of compressed air into the other. The specimen was immersed in saline solution and the pressure noted when bubbles appeared.

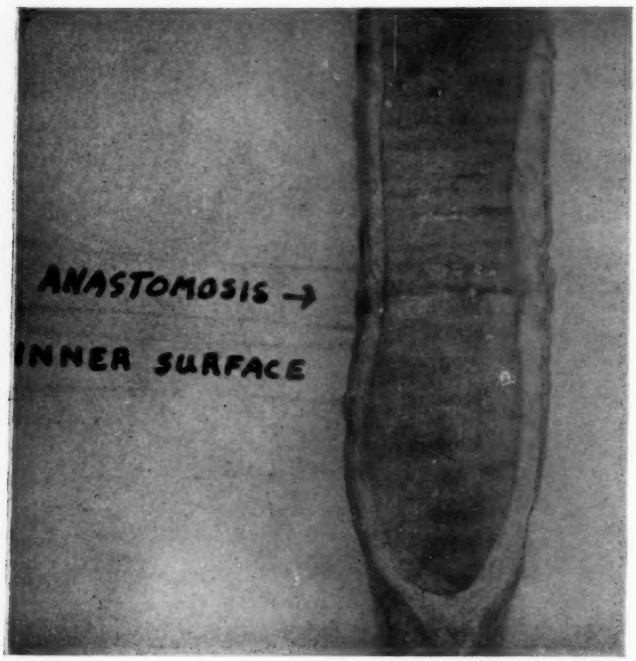


Fig. 3.—Anastomosis from dog sacrificed four months after resection of 5.0 cm. of the trachea. Catgut; tension 230 Gm.

The lowest pressure at which leakage occurred, usually through a needle hole, was 70 mm. Hg. Most of the anastomoses withstood 300 mm. Hg. In other specimens, where the mucosal cuff was omitted, the union could be made equally airtight by including adjacent muscle in the sutures. These are much higher pressures than are likely to occur under natural circumstances, and leakage was not observed in anastomoses made by these methods in living animals.

An evenly matched tracheobronchial anastomosis, on either side, can be made end-to-end by the first method described above in either dogs or human beings (cadavers). The difference in diameters is easily adjusted by stretching the bronchial posterior membrane, and suturing it to both ends of the tracheal cartilage as well as to the tracheal membrane, which remains contracted (Fig. 10, *c*).

Friability of the tissues to be sutured may be encountered in the diseased trachea. Experimentally, this condition was found in several instances where repeated resections of the same trachea were done, especially if the interval was 3 weeks or elss, and if an unsuccessful attempt at reconstruction or a poor type of anastomosis had been made. Mattress sutures through the annular ligament tore out repeatedly under such conditions; even the cartilage seemed softer than normal, and it tore or split if the suture was passed through it. Anastomosis could be made, however, either by the method previously described, or by passing sutures around intact rings, as advised by Nach and Rothman (1943).

Fig. 4.

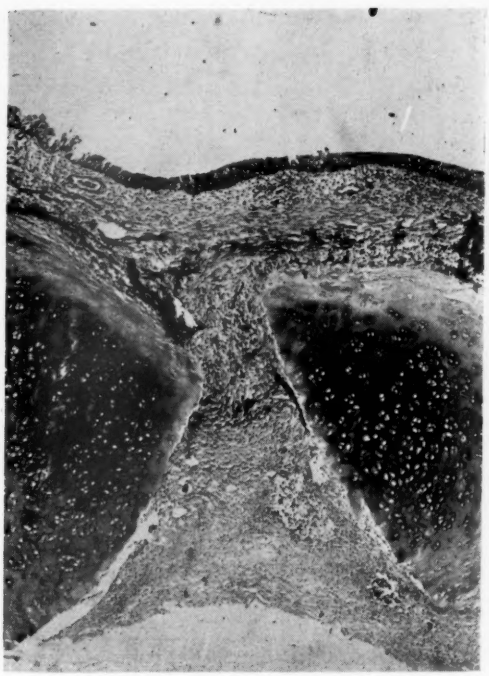


Fig. 5.

Fig. 4.—Photomicrograph of anastomosis from larger specimen shown in Fig. 2. Eighth postoperative day.

Fig. 5.—Photomicrograph of tracheal anastomosis sixteen days after operation. Catgut; tension 200 Gm.

The remaining difficulty of those just listed—stricture formation—will be discussed subsequently.

Tracheal Resections.—Resection and anastomosis of the cervical trachea were carried out 58 times in dogs. When freed up and stretched, the trachea carries its blood supply from above and below, and in all anastomcses there was free bleeding at both ends. In 36, the mucosal cuff was fashioned as described. A few minor protrusions of scar tissue and some granulomas with extruding silk, such as those seen in Fig. 14, were the only complications (Table I). The typical gross and microscopic appearance of these anastomoses may be seen in Figs. 2 through 6.

TABLE I. THIRTY-SIX TRACHEAL RESECTIONS, ANASTOMOSES MADE WITH MUCOSAL CUFF; SECOND AND THIRD RESECTIONS ARE INCLUDED*

	WEIGHT (KG.)	INITIAL TENSION (GM.)	LENGTH RESECTED (CM.)	FINAL TENSION (GM.)	POSTOP. DAY EXAM.	TYPE OF EXAMINATION		RESULTS				
						GROSS AND MICROSCOPIC	BRONCHOSCOPY AND PALPATION	STENOSIS	PROTRUSION OF SCAR	GRANULATION	SUTURES IN LUMEN	STRETCHING OF SCAR
1	20	100	3.8	195	63	×						×
2	20	150	2.6	300	102	×						
3	25	95	5.0	230	121	×						
4	16	90	4.0	190	142	×						
5	18	90	4.1	340	98	×						
6	21	90	4.2	270	126	×						
7	18	95	5.1	260	109	×						
8	16	62	4.5	200	16	×						
9	20	80	4.9	225	81	×						
10	14	40	4.5	220	24	×						
11	20	100	5.2	330	101	×			×			
12	10	60	4.4	260	16	×						
13	17	75	5.0	270	52	×			×	×	2	
14	21	80	4.7	300	50	×						
15	26	45	4.7	200	55	×				×	2	
16	12	60	4.5	200	67	×				×	2	
17	17	95	5.6	290	5	×						
18	10	70	3.0	100	47	×						
19	16	200	6.2	900	20	×						
20	12	30	2.0	50	15	×			×			
21	30	70	1.4	95	8	×						
22	12	70	1.5	100	4	×						
23	9	50	1.2	70	8	×						
24	14	80	1.2	110	4	×						
25	19	50	6.0	550	20	×						
26	30	90	3.2	500	24		×					
27	23	110	5.5	350	58		×		×		1	
28	20	50	4.3	250	38	×			×			
29	14	100	4.6	220	38		×			×	1	
30	16	90	4.8	300	36		×			×	3	
31	15	80	6.0	500	15		×					
32	20	65	8.8	650	57	×						
33	21	100	2.8	250	6	×						
34	12	100	4.2	300	52		×					
35	21	200	3.0	500	50		×			×	2	
36	16	450	2.2	1000†	54	×						

*First twelve sutured with catgut, remainder with interrupted silk.
†Head flexed slightly.

*First twelve sutured with catgut, remainder with interrupted silk.
†Head flexed slightly.

TABLE II. TWENTY-TWO TRACHEAL RESECTIONS; ANASTOMOSES MADE WITHOUT MUCOSAL CUFF; SECOND AND THIRD RESECTIONS ARE INCLUDED*

	WEIGHT (KG.)	INITIAL TENSION (GM.)	LENGTH RESECTED (CM.)	FINAL TENSION (GM.)	POSTOP. DAY EXAM.	TYPE OF EXAMINATION		RESULTS				
						GROSS AND MICROSCOPIC	BRONCHOSCOPY AND PALPATION	STENOSIS	PROTRUSION OF SCAR	GRANULATION	SUTURES IN LUMEN	STRETCHING OF SCAR
1	20	130	0.2	130	168	×						
2	24	105	1.5	120	64	×						
3	15	70	3.8	195	91	×		×				×
4	15	90	3.0	220	71	×		×				×
5	12	90	4.5	200	32	×		×		×	×	×
6	19	110	4.4	345	30	×				×	2	
7	14	100	3.5	200	49	×				×		
8	12	50	1.8	150	30	×				×		
9	9	65	2.0	125	10	×				×	×	×
10	15	75	3.0	450	5	×				×		
11	19	65	2.3	200	10		×					
12	9		4.0	265	5	×				×	×	Disrupted
13	20	150	2.0	350	18		×					
14	13	70	3.8	600	14		×					
15	18	150	1.7	350	17		×					
16	6	45	3.0	150	17		×			×		
17	18	150	1.7	350	19		×			×		
18	15	75	3.0	450	6	×				×	×	
19	20	250	2.0	450	14		×			×		
20 R	11	50	1.1	75	7	×			×	×		×
20 L					7	×						
21 R	14	70	1.3	120	7	×			×	×	×	×
21 L					7	×			×	×		
22 R	15	140	1.9	220	41	×			×			×
22 L					41	×						

*1 to 6, tracheas divided through cartilage, no cuff; 7 to 19, tracheas divided through annular ligament, silk mattress sutures; 20 to 22, tracheas divided through cartilage, cuff on left side, none on right.

In the other 22 operations the mucosal cuff was omitted, which meant that there was a 2 to 6 mm. gap in the mucosa on completion of the anastomosis. The trachea was cut through the cartilage and mucosa at the same level in 6 instances, and sutures passing around the segments of ring were visible in the lumen. The anastomosis was made leak-proof by including muscle in the sutures. In 3 dogs a mucosal cuff was retained on the left side only. In the remaining 13 operations in this group, the trachea was divided through the annular ligament and anastomosed with mattress sutures. The silk passed through the cartilages posteriorly where they flare out.

Fig. 6.—Photomicrograph of tracheal anastomosis fifty-five days after operation. Interrupted silk; tension 200 Gm. New cartilage is surrounding the divided rings.

Results on the whole were less satisfactory in the second of the 2 groups (Table II). Some strictures developed, though they did not cause signs of obstruction. In the dogs with mucosal apposition on only 1 side, that side healed better in each instance (Table II).

At the conclusion of the experiments the dogs still living with tracheal anastomoses were evaluated by means of bronchoscopy and palpation of the suture line through the neck.

There was no mortality from tracheal resection; no dog died within 2 weeks of the operation, or at any time as a result of it.

Suture Material.—Twenty-day chromic catgut, size 000, was used for 18 anastomoses and gave excellent results in all but 2, where there was undue

TABLE III. CHANGES IN TENSION AT THE ANASTOMOSIS WITH SECOND AND THIRD RESECTIONS OF THE SAME TRACHEA

		FIRST RESECTION				SECOND RESECTION				THIRD RESECTION		
	WEIGHT (KG.)	INITIAL TENSION (GM.)	LENGTH RESECTED (CM.)	FINAL TENSION (GM.)	INTERVAL (DAYS)	INITIAL TENSION (GM.)	LENGTH RESECTED (CM.)	FINAL TENSION (GM.)	INTERVAL (DAYS)	INITIAL TENSION (GM.)	LENGTH RESECTED (CM.)	FINAL TENSION (GM.)
1	15	70	3.8	195	91	85	3.0	220	71	90	3.0	450
2	20	100	3.8	195	63	150	2.6	300	102	250	2.0	450
3	14	70	1.3	120	7	100	3.5	200				
4	17	140	1.9	220	41	200	6.2	900	20	450	2.2	1000+*
5	21	90	4.2	270	126	100	2.8	250	6	200	3.0	500
6	18	95	5.1	260	109	150	1.7	350				
7	20	100	5.2	330	101	150	2.5	350				
8	13	60	4.5	200	67	70	3.8	600				
9	12	30	2.0	50	15	50	1.8	150				
10	30	70	1.4	95	8	90	3.2	500				
11	9	50	1.2	70	8	65	2.0	125				
12	19	110	4.4	345	30	65	2.3	200				
13	15	90	4.0	190	142	120	3.0	290				

*Head flexed slightly.

TABLE IV. VARIOUS ATTEMPTS AT RECONSTRUCTION OF SEGMENTS OF THE CERVICAL TRACHEA IN EIGHTEEN DOGS

TYPE OF OPERATION	DOG NO.	WEIGHT (KG.)	LENGTH RESECTED (CM.)	TENSION (GM.)	GUT OR SILK	POSTOP. DAY EXAM.	STENOSIS	PROTRUSION OF SCAR	SLOUGH	PNEUMONIA
Tracheal homograft	1	10	1.6		g	8	×		×	×
	2	17	1.8		s	69	×		×	×
	3	17	1.7		s	31	×		×	×
	4	26	1.9		s	38	×		×	×
	5	16	1.8		s	16	×		×	
	6	18	1.7		s	16	×		×	
	7	25	1.6		g	24	×		×	×
Tracheal autograft	8	14	1.6	100	s	20	×		×	
	9	12	2.9	85	s	8			×	
	10	15	2.6	95	g	15	×		×	×
	11	7	2.0	70	g	22	×		×	
Costal cartilage	12	20	1.6		g	13	×			
Aortic homograft	13	6	1.6		g	4	×		×	×
	14	4	2.0	25	g	6	×		×	
Tantalum gauze tube	15	11	1.6	75	s	42	×			×
	16	16	1.3	70	s	9		×		
	17	14	1.6	100	s	30	×			
	18	12	1.6	125	s	20		×		

stretching of the scar (1 tracheal and 1 tracheobronchial). In a few others there was a little separation of the rings on 1 side, indicating that the suture had broken prematurely. The catgut was interrupted at 4 places around the trachea.

Anastomoses made with interrupted 0000 silk did not show any stretching of the scar. However, the sutures frequently worked their way into the lumen, or they had been passed through the mucosa unintentionally, causing granulomas which healed as small fibrous protrusions when the silk was completely extruded (Fig. 14). Since the mucosa healed promptly between and over most of the sutures, strictures did not result from this process. The silk was more reliable, but gave a less satisfactory scar than was usually the case with catgut.

Stenosis.—Stricture formation at the site of anastomosis has been recognized from the earliest experiments.[3] It may be defined for our purposes as narrowing of any diameter of the tracheal lumen to ⅔ or less of normal. Signs of obstruction, such as stridor, were not observed in any animal until the diameter of the lumen was reduced to ¼ or less of normal, but less severe strictures may prove troublesome if a respiratory infection develops.

Severe stenosis occurred in nearly all the attempts at tracheal reconstruction by means of grafts (Table IV), but was uncommon with end-to-end anastomosis. In the latter group it was the result in 3 cases where the mucosa had not been approximated. In these 3 instances mucosa slowly covered the granulating area, after which the lumen was not further narrowed; in 1, appreciable widening of the stenotic area was observed bronchoscopically over a period of weeks after the mucosa healed. Two of the 3 are shown in Fig. 9.

Healing Properties of Tracheal Mucosa.—From the foregoing it appeared that the tracheal mucosa did not bridge small gaps very rapidly. To test this

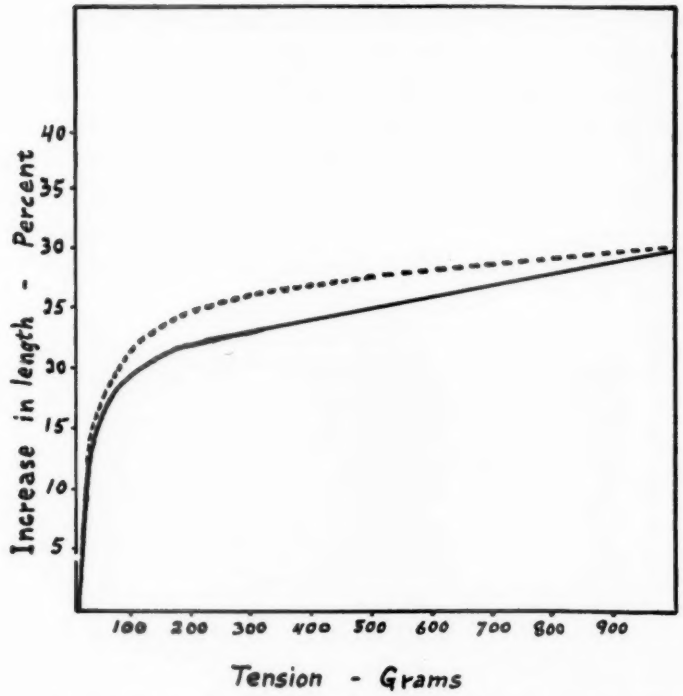


Fig. 7.—Increase in length produced by varying tension on excised human (broken line) and canine (solid line) tracheas. Average from ten in each group.

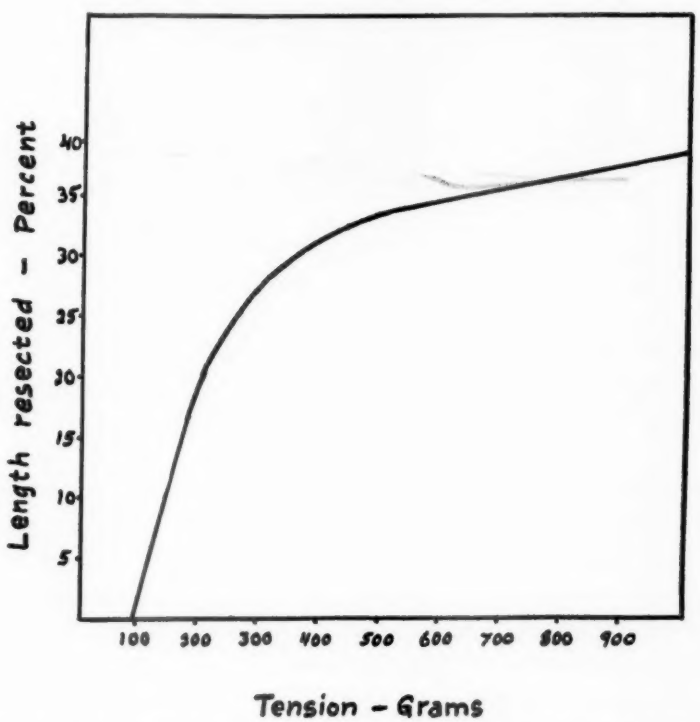


Fig. 8.—Length of trachea which can be resected in per cent of the total length, in relation to the tension on the anastomosis. Data from operations on dogs.

assumption further, the following experiment was performed in 8 dogs. The anterior wall of the cervical trachea was incised longitudinally through 6 rings, and a circumferential strip of mucosa 1 cm. in width was removed. It did not strip off easily, and small injuries to the perichondrium of the 2 underlying rings occurred. No tracheal blood vessels were ligated; bleeding was stopped by maintaining pressure for a few minutes.

Two of the dogs were then operated on again at each of 5, 10, 15, and 20 day intervals, at which times 8 or 10 rings were resected, including the area of mucosal excision.

Fig. 9.—Resected tracheal segments from two dogs, showing stricture formation at the site of anastomosis. Upper specimen thirty-two days and lower specimen seventy-one days after operation. Mucosal cuff was omitted. Upper, silk; lower, catgut; tensions 200 and 220 Gm.

Specimens removed at 5 days showed no gross or microscopic growth of epithelium. A small amount of granulation tissue could be seen at the edges of the wound. The cartilage was bare in some areas where the perichondrium had been destroyed.

At 10 days there was more granulation tissue, but bare cartilage was still visible. There was less than 1 mm. of new epithelium growing from the edges of the wound as a single layer of nonciliated cells.

At 15 days 1 specimen showed a thin layer of granulation tissue, covered over one-half its extent by a single layer of nonciliated epithelial cells. The other specimen contained a large, protruding area of granulations, with very little growth of epithelium from the edges. The lumen was reduced to less than ⅓ of normal, partly, however, due to straightening out of the divided rings. Bits of necrotic cartilage were present in the granulations.

One of the 20 day specimens appeared to be nearly healed with little change in size of the lumen. Microscopically there was a single-celled layer of epithelium over most of the excised area. Granulating areas containing bits of necrotic cartilage were also present, however. The other trachea showed a very firm stricture, especially posteriorly. The lumen measured 2 by 10 mm. Microscopically there was abundant new connective tissue with only a small growth of epithelium at the edges.

In general, the growth of epithelium was not especially rapid. Sloughing of unprotected bits of cartilage probably interfered to some extent with healing.

Length Resectable.—The question how much of the trachea can be resected, with resuture, naturally arises. Nowakowski gave a figure of 3 to 5 cm. from his studies on adult human cadavers. About twice this much can be removed from dogs. The resectable length in a given instance depends on the elasticity of the trachea, the mobility of the larynx and hilar structures, and the position of the head and neck.

The elasticity of the trachea was measured in the following way. Tracheas excised from 10 dogs and from 10 human cadavers were measured in the resting state and then suspended from the cricoid cartilage. Graduated weights were then attached to the carina. The resulting increase in length is shown graphically in Fig. 7.

The greatest increase in a dog's trachea was 45 per cent, in a young dog weighing 15 kg.; the smallest, 14 per cent in an old dog weighing 30 kg. Corresponding values in the human tracheas were 35 per cent in a woman aged 28, and 17 per cent in a man aged 76, both being of average size. It is apparent from Fig. 7 that most of the stretch obtainable is reached in both species at a tension of about 200 Gm.

Measurements were made in living dogs of the tension required to bring the divided ends of the trachea together after successively longer segments were removed. The per cent of length resected was calculated by assuming that the total length of the trachea at the initial tension was the same as that of an excised trachea from a dog of similar size under the same tension. These data are shown graphically in Fig. 8; when compared with the measurements from excised tracheas, they indicated that mobility of larynx and carina is of importance in obtaining the resectable length. The carina is less mobile in the human being than in the dog.

In the living dog most of the resectable length is obtained at a tension of about 450 Gm. at the anastomosis. At this tension aortic pulsation is readily felt on the lower segment, and any greater pull on the upper segment tends to bend the neck forward.

It has just been shown that anastomoses can stand, at least initially, 35 to 40 times this much tension. In the 11 dogs in which suture of the trachea was performed at 450 Gm. tension or more, healing was satisfactory. Of course the tension varied greatly with movement of the head and neck; it was at times greater than the measured amount, as the dogs showed no restraint in extending and stretching their necks after operation.

Serious disruption of the anastomosis occurred in only 1 dog, in which an interrupted mattress suture was placed in the annular ligament at a tension of 265 Gm. This was a second resection, and the tissues were somewhat friable.

Permanent elongation of the trachea, due to stretching of the annular ligaments, was observed in dogs undergoing second and third resections. At the second and third operations the initial tension was considerably less than the tension at which the previous anastomoses had been made (Table III). Therefore more length could be removed in stages than at 1 operation. In these

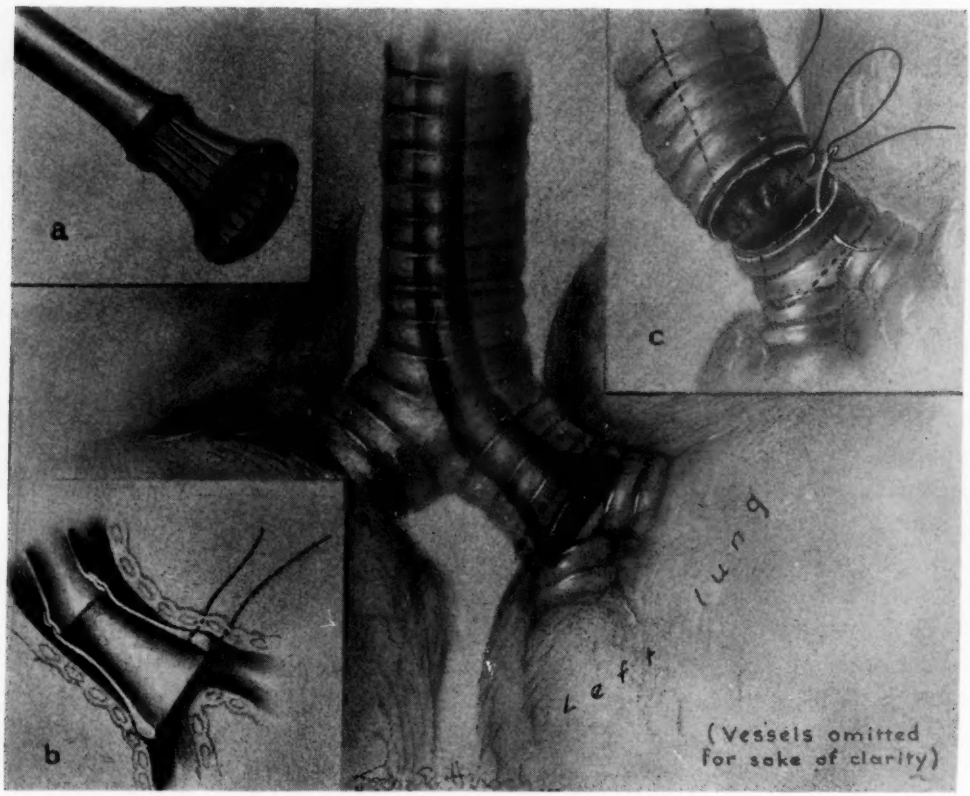


Fig. 10.—Drawing illustrating a method of tracheobronchial anastomosis. The tip of the breathing tube (*a*) is of thin rubber reinforced with spring wires soldered to a metal ring at the proximal end. The distal rubber ring is sutured into the bronchus with three to five temporary sutures (*b*). The vessel to the right lung having been ligated and divided, the trachea and left bronchus are cut across through the cartilaginous rings, as indicated by the dotted lines. The intervening segment is removed, together with the right lung, by incising the posterior membrane. Anastomosis is then made (*c*) as described in the text. Mucosal cuffs are retained at each end to be sutured. The tube is withdrawn when the anastomosis is complete.

experiments the longest piece excised was 8.8 cm. (16⅓ rings), or 41 per cent of the estimated length of the trachea. The greatest total amount removed in three stages was 10.3 cm. (18 rings), or 46 per cent.

Tracheobronchial Anastomosis.—In order to perform such an operation unhurriedly in a living animal, an air tube may be fastened into the distal part of the primary bronchus (Fig. 10, *a* and *b*). Conical endpieces of varying size were made from natural latex by dipping.* Thick rings of rubber are

*Acknowledgment is made to the American Anode Company, Inc., of Akron, Ohio, for materials and technology of latex dipping.

formed at the open end, from which thin walls taper to the point of attachment of the air tube. The walls are supported by 9 spring wire loops, soldered to a metal ring at the proximal end. The wire is 0.011 inch in diameter. The endpiece, which is firmly attached to a rubber or plastic breathing tube of about 4.5 mm. internal diameter, may be folded up inside an ordinary intratracheal tube for introduction; it regains its proper shape, and the rubber ring at the end, 18 to 21 mm. in diameter, fits snugly into the bronchus to be anastomosed.

Fig. 11. Fig. 12.

Fig. 11.—Anterior view of tracheobronchial anastomosis in a dog, sixty-five days after operation. Catgut, left side.

Fig. 12.—Same specimen as Fig. 11, opened posteriorly to show inner surface.

It is essential to suture the tube securely in place, with from 3 to 5 sutures passing around the rubber ring and through the thin wall of the endpiece (Fig. 10, *b*). The sutures are removed when the anastomosis is complete, and the tube is withdrawn. The conical shape of the endpiece leaves room for division and suture of the bronchus just proximal to the rubber ring. The proximal part of this bronchus, the opposite lung, together with the carina and a 2.5 cm. segment of the lower trachea may then be removed en bloc, cutting the posterior membrane to get around the tube.

This operation was performed in 8 dogs; in 5 the right lung, and in 3 the left was removed. Two of the dogs died, 25 and 28 hours after operation, of

atelectasis due to plugging of the secondary bronchi with secretion. The other 6 dogs recovered rapidly. Four of them have been sacrificed while in good health at intervals of from 28 to 65 days after operation. The remaining 2 are living and well after 13 months, at which time bronchoscopy shows apparently well-healed anastomoses.

Six of the operations were done with catgut and 2 with silk. Tension on the anastomosis was about 200 Gm. in each case. In 1 of those where catgut was used the scar had stretched to about 1 cm. in length at 28 days. The others were well healed (Figs. 11 through 14).

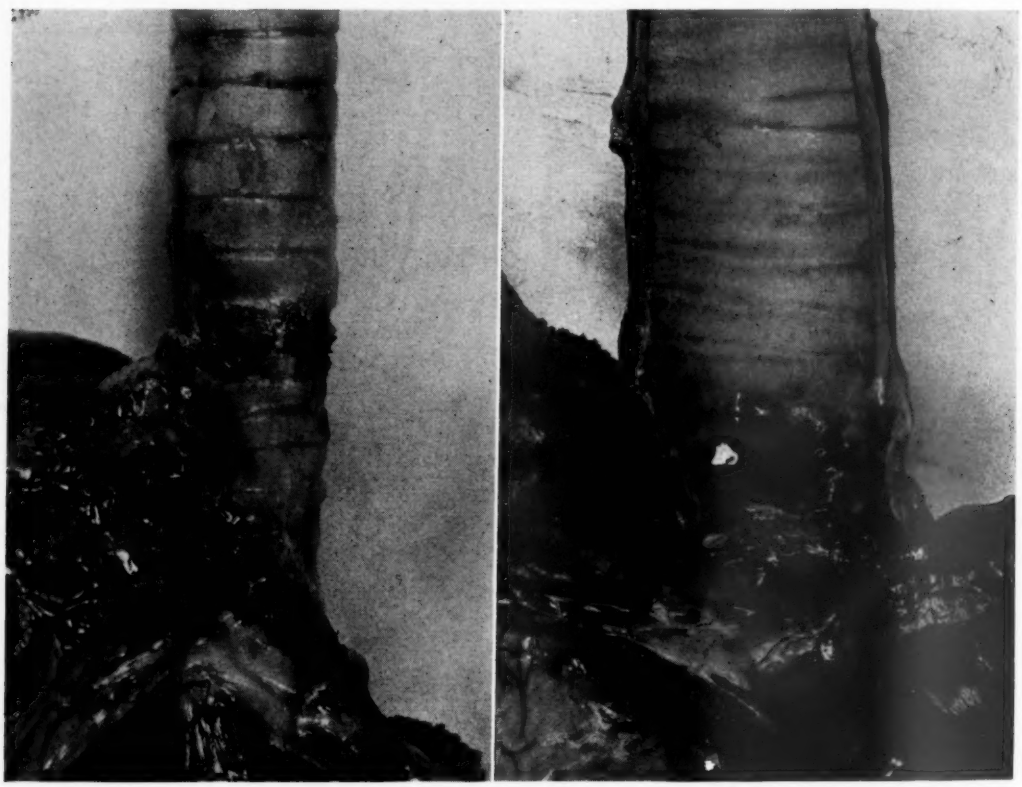


Fig. 13. Fig. 14.

Fig. 13.—Right tracheobronchial anastomosis in a dog, fifty-two days after operation. Interrupted silk; tension 200 Gm.

Fig. 14.—Same specimen as Fig. 13, opened posteriorly to show inner surface.

Tracheal Homografts.—Segments of the cervical trachea in 7 dogs were excised and replaced by similar segments from other dogs. The grafts were 1.5 to 2.0 cm. in length. Anastomoses were made with a mucosal cuff as described previously, using silk in 4 and catgut in 3. The grafts in 2 dogs were segments exchanged from 1 to the other at the same operation. In four instances the grafts were kept refrigerated in sterile saline solution containing 500 units of penicillin per cubic centimeter for from 1 to 4 days. One graft was put in saline solution and heated to boiling for 5 minutes.

The wounds healed well, and for a time the dogs appeared healthy. Bronchoscopic examinations after 7 to 10 days showed disappearance of the transplanted mucosa, bare cartilaginous rings, and granulation tissue at the suture lines. The graft which was heated showed sloughing of the mucosa in 2 days, and the transplanted rings were coughed out on the fifth day.

The dogs survived from 8 to 69 days after operation. All developed severe stenosis and died of tracheal obstruction and pneumonia. The grafted area was a mass of scar tissue; in 3 dogs dying after 1 month no grossly recognizable elements of the transplant were present. Microscopic sections showed a mass of connective tissue containing bits of necrotic cartilage. There was no epithelial covering.

Tracheal Autografts.—Autografts were performed in 4 dogs by resecting a segment 1.5 to 2.0 cm. in length from the cervical trachea and immediately suturing it back in place, discarding 2⅔ rings to permit the use of mucosal cuffs at each end. Tension on the anastomosis was 70 to 100 Gm. Silk sutures were used in 2 and catgut in 2.

After 8 days the graft was grossly intact except that the mucosa was discolored. Microscopic section showed that some of the mucosa in the graft was apparently living, but large areas were necrotic (Fig. 15).

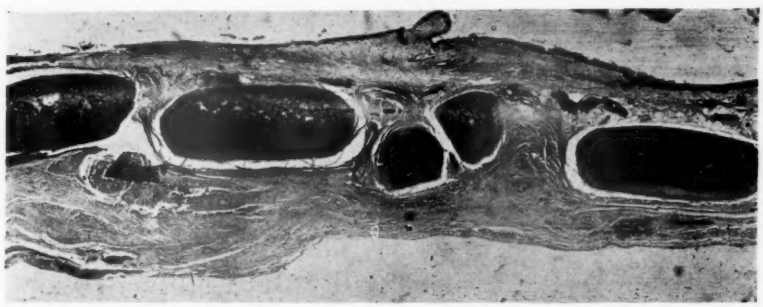


Fig. 15.—Photomicrograph of tracheal autograft, eight days after operation. Part of the graft is seen at the left of the anastomosis, which appears to be healing. There is necrosis at the left end of the section.

The other 3 dogs developed severe stridor and cough after 15, 20, and 22 days, and resection of the grafted area was performed. There was marked fibrous stenosis, with almost complete disappearance of the graft. Microscopic sections showed granulation tissue, necrotic cartilage, and no epithelial growth.

As it is well known that cartilage grafts must be well nourished on all sides if they are to survive,[21, 22] it could hardly be expected that tracheal grafts would live. The hope that the transplant would survive long enough for new cartilage and mucosa to bridge the gap was not realized.

Costal Cartilage Transplant.—In 1 dog a segment of cervical trachea 1.5 cm. in length was removed and the free ends of the trachea were sutured with catgut to the adjacent muscles. Two of the lower costal cartilages, each 3 cm. in length, were excised from each side of the same animal and embedded immediately in the neck muscles, bridging the tracheal gap a few mm. from the lumen. They were arranged parallel with the trachea and equally distant from each

other, in a manner designed to prevent herniation of the muscle into the trachea. It was thought that the muscle would provide a good bed for the growth of tracheal mucosa across the gap.

The wound healed normally. After 10 days there was stridor and cough; 3 days later the obstruction was nearly complete and the animal was sacrificed. The gap between the ends of the trachea was shortened and filled by a firm, fibrous stricture growing in from the muscle (Fig. 16). There was no evidence of infection in the wound and the costal cartilages appeared to be healing in place.

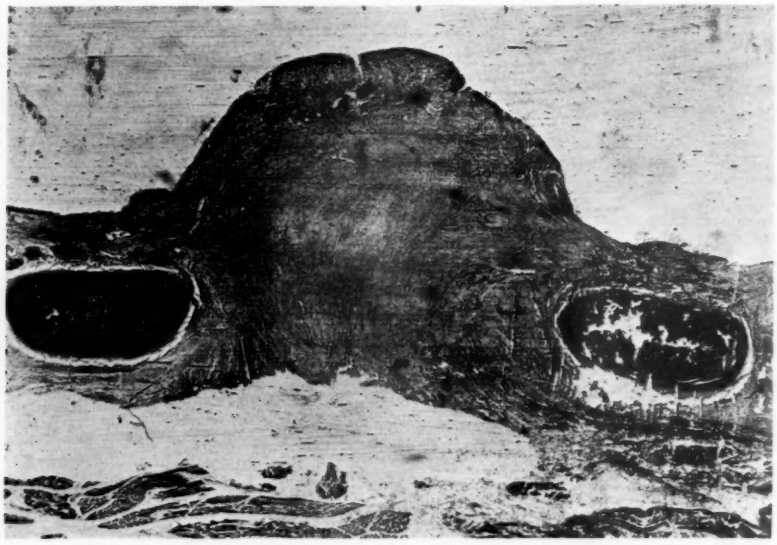


Fig. 16.—Photomicrograph of tracheal reconstruction with costal cartilage and muscle, thirteen days after operation. The mucosa has made little progress. Death due to tracheal stenosis.

Aortic Transplants.—Pieces of aorta were transplanted into tracheal defects in 2 dogs. They were obtained from large dogs freshly killed, and were refrigerated a few hours in saline-penicillin solution before being used. Segments 1.6 and 2.0 cm. in length were excised from the cervical tracheas of 2 very small dogs, and were replaced by pieces or aorta of equal length and diameter. Tension on the anastomoses was 40 and 25 Gm., which was sufficient to hold the lumen open. One dog died after 3 days, and the other after 6 days. The grafts both sloughed out and obstructed the trachea.

Tantalum Gauze.—Tracheal segments in 4 dogs were excised from the neck and replaced with tantalum gauze,[36] 0.003 inch 50 mesh. The gauze was bent into a tube 3.2 cm. long, and fitted over the ends of the trachea, which were separated 1.6 cm. in each case. The gauze overlapped 1½ rings at each end, and was sutured to the annular ligaments with interrupted silk. The gauze quickly became impregnated with fibrin, and when the neck muscles were sutured over it, there was very little leakage.

Specimens were resected at 9, 20, and 42 days. At 9 days the gauze was firmly held in place by fibrous tissue. Most of the luminal surface was covered

with a thin layer of granulation tissue. At 20 days the appearance was similar, and there was only a small area where the gauze was bare. The epithelium, however, had made little or no progress.

At 42 days cough and stridor were present and the lumen was narrowed to 3 or 4 mm. in diameter by a fibrous stricture, over which there was no epithelium. The gauze was bent inward on each side and was firmly embedded in the scar except for 2 small patches which were bare on the luminal surface.

One dog is still living. Bronchoscopy at 30 days shows beginning stricture formation.

DISCUSSION

The surgical problems involved in tracheal resection and anastomosis appear to be relatively simple and easily solved. Resection of the trachea was recognized many years ago as the best treatment for benign strictures. It was suggested by Scott (1928), following his successful suture of an accidental transverse division of the trachea, that section and resuture of the trachea might be worth while to obtain exposure of the esophagus.

Tumors of the trachea, which are uncommon,[9] are most often treated by partial excision, fulguration, or irradiation.[34] It would be better to remove them completely, because malignancy may be overlooked, or may develop later.[5] It would appear from these studies that any tumor involving ¼ to ⅓ of the trachea or less could be safely treated by total excision and anastomosis.

Bronchogenic carcinoma is generally considered inoperable when it involves the trachea or carina.[31] In suitable cases a tracheobronchial anastomosis would permit resection of this area along with the involved lung. Penetration of the trachea over a limited area by carcinoma arising in the esophagus should not in itself render the lesion inoperable.

The problem of tracheal reconstruction is much more difficult, and has not been entirely solved. Though some success has been reported with the use of rigid tubes, difficulties were apparent. There was always the danger, for example, that the tube would unexpectedly come loose and obstruct the airway. None of the present attempts at reconstruction succeeded, but in every instance more than the reconstructed segment could easily have been resected, with anastomosis. Apparently the 2 ends of normal trachea properly sutured together will heal satisfactorily under much greater tension and with less likelihood of stenosis than will trachea sutured to the other viable or nonviable structures so far tested.

SUMMARY AND CONCLUSIONS

Tracheal resection and anastomosis have been studied in a series of 58 operations on dogs. A method of anastomosis affording accurate approximation of the mucosa and maximal tensile strength is described. Use of this method in resections up to 8.8 cm. in length resulted in no strictures or other serious complications. There was no mortality.

The development of stenosis at the suture line was invariably associated with failure to approximate viable mucosal edges. Evidence is presented that the tracheal mucosa does not always cover small defects rapidly.

As a general rule, from ¼ to ⅓ of the tracheal length can be safely excised with end-to-end anastomosis. In the dog most of the resectable length is obtained at a tension of about 450 Gm. at the anastomosis, with the head in neutral position. Permanent elongation of the trachea can occur, and more length can be removed in stages than at 1 operation.

Resection of 1 lung, part of the opposite bronchus, and the lower trachea and carina was carried out in 8 dogs, with end-to-end tracheobronchial anastomosis. Although 2 of the dogs were lost on the first postoperative day from atelectasis, the other dogs remained in good health until sacrificed. The anastomoses healed satisfactorily.

Attempts at reconstruction of short tracheal segments in 18 dogs by means of tracheal homografts, tracheal autografts, free transplant of costal cartilage, aortic grafts, and tantalum gauze, were all unsuccessful.

The comparative ease and safety of tracheal resection and anastomosis suggest that where indicated this operation may properly be used in place of less effective measures.

REFERENCES

1. Bruns, P.: Resektion der Trachea bei primären Trachealkrebs, Beitr. z. klin. Chir. 21: 284, 1898.
2. Carter, M. G., and Strieder, J. W.: Resection of the Trachea and Bronchi, Abstract, To be published.
3. Clagett, O. T., Grindlay, J. H., and Moersch, H. J.: Resection of the Trachea, Arch. Surg. 57: 253, 1948.
4. Colley, F.: Die Resektion der Trachea, Deutsche Ztschr. f. Chir. 40: 150, 1895.
5. Crafoord, C., and Lindgren, A. G. H.: Mucous and Salivary Gland Tumors in the Bronchi and Trachea, Acta chir. Scandinav. 92: 481, 1945.
6. Daniel, R. A.: The Regeneration of Defects of the Trachea and Bronchi, J. Thoracic Surg. 17: 335, 1948.
7. Davis, J. S.: The Transplantation of Free Flaps of Fascia, Ann. Surg. 54: 734, 1911.
8. Eiselsberg, A.: Zur Resktion und Naht der Trachea, Deutsche med. Wchnschr. 22: 343, 1896.
9. Ellman, P., and Whittaker, H.: Primary Carcinoma of the Trachea, Thorax 2: 153, 1947.
10. Erich, J. B.: Treatment of Extensive Cicatricial Stenosis of the Larynx or the Trachea, Arch. Otolaryng. 41: 343, 1945.
11. Föderl, O.: Zur Resektion und Naht der Trachea, Wien. klin. Wchnschr. 9: 1258, 1896.
12. Gluck, Th., and Zeller, A.: Die Prophylactische Resektion der Trachea, Arch. f. klin. Chir. 26: 427, 1881.
13. Grosse: Trachealknorpeldefekt und Silberdrahtnetzdeckung, Centralbl. f. Chir. 28: 1110, 1901.
14. Hacker, E.: Resektion der Luftröhre mit Primärer cirkulärer Naht wegen hochgrodiger ringförmiger Narbenstriktur, Beitr. z. klin. Chir. 32: 709, 1902.
15. Hohmeier: Ueber ein neues Verfahren zur Deckung von Trachealdefekten, München. med. Wchnschr. 58: 948, 1911.
16. König, F.: Zur Deckung von Defekten in der Vorderen Trachealwand, Berl. klin. Wchnschr. 33: 1129, 1896.
17. König, F.: Ersatz eines grossen Trachealdefectes, Verhandl. d. deutsch. Gesellsch. f. Chir. 26: 95, 1897.
18. Kostenko, M. F., and Rubaschew, S. M.: Ueber die freie Fascientransplantation (Abstr.), Zentralbl. f. Chir. 39: 1448, 1912.
19. LeJeune, F., and Owens, N.: Chronic Laryngeal Stenosis, Ann. Otol. Rhin. & Laryng. 44: 354, 1935.
20. Levit, H.: Deckung von Trachealdefecten durch eine freie Plastik aus der Fascia lata femoris, Arch. f. klin. Chir. 97: 687, 1912.
21. Loeb, L.: Autotransplantation and Homoiotransplantation of Cartilage in the Guinea Pig, Am. J. Path. 2: 111, 1926.
22. Loeb, L.: Autotransplantation and Homoiotransplantation of Cartilage and Bone in the Rat, Am. J. Path. 2: 315, 1926.

23. Longmire, W. P.: The Repair of Large Defects of the Trachea, Ann. Otol. Rhin. & Laryng. **57:** 875, 1948.
24. Lucas, H.: Ueber die freie Plastik der Fascia Lata, Arch. f. klin. Chir. **100:** 1129, 1913.
25. Maisel, B., and Dingwall, J. A.: Primary Suture of the Divided Cervical Trachea, SURGERY **27:** 726, 1950.
26. Morris, Henry: Morris' Human Anatomy, ed. 10, Philadelphia, 1942, The Blakiston Company, p. 1401.
27. Naih, R. L., and Rothman, M.: Injuries to the Larynx and Trachea, Surg., Gynec. & Obst. **76:** 614, 1943.
28. Neuhof, H.: Fascia Transplantation Into Visceral Defects, Surg., Gynec. & Obst. **24:** 383, 1917.
29. Niehues: Ueber die Behandlung von Larynxstenosen und Trachealdefekten, Zentralbl. f. Chir. **30:** 846, 1903.
30. Nowakowski, K.: Beitrag zur Tracheoplastik, Arch. f. klin. Chir. **90:** 847, 1909.
31. Ochsner, A., DeBakey, M., Dunlap, C. E., and Richman, I.: Primary Pulmonary Malignancy, J. Thoracic Surg. **17:** 573, 1948.
32. Scott, G. D.: Extensive Cut-Throat With Complete Laceration of Trachea and Esophagus, J. A. M. A. **90:** 689, 1928.
33. Taffel, M.: The Repair of Tracheal and Bronchial Defects With Free Fascia Grafts, SURGERY **8:** 56, 1940.
34. Tinney, W. S., Moersch, H. J., and McDonald, J. R.: Tumors of the Trachea, Arch. Otolaryng. **41:** 284, 1945.
35. Trnka: Eine praktische Methode der Tracheoplastik mit gedoppelten Hautlappen, Centralbl. f. Chir. **27:** 413, 1900.
36. Venable, C. S., and Stuck, W. G.: A General Consideration of Metals for Buried Appliances in Surgery, Internat. Abstr. Surg. **76:** 297, 1943.

Book Reviews

Chirurgie De L'Uretre. L. Sabadini, Professor of Urology, Faculty of Medicine, Algiers. Pp. 373, with 411 illustrations. Paper covered, in French. Paris, 1949, Masson & Cie.

The author, who is Professor of Urology at the Faculty of Medicine in Algiers, points out that disease and injuries of the urethra are very prevalent in North Africa, as indeed they must be to furnish the wealth of material for this book. The author states in his foreword that the work is intended to be practical rather than didactic, and it is, there being no formal references to the literature.

He discusses the anatomy and examination (largely by urethrography) of the urethra, then goes on to ruptures of the urethra, their complications and treatment. Next come wounds of the urethra and glans penis (the latter mainly from ritual circumcision), then the surgical complications of gonorrhea, including prostatic abscess. Strictures and extravasation are discussed at some length, and there is a brief discussion of cancer of the penis.

One may summarize the author's attitude briefly by saying that he favors the excision, wherever possible, of a badly traumatized, strictured, or inflamed segment of the urethra, followed by plastic closure or anastomosis over a catheter supplemented by suprapubic drainage. There are many excellent diagrams and innumerable urethrograms, both pre- and postoperative, most of the latter showing excellent results. Urethral and prostatic calculi are removed by open operation, but Sabadini points out that, during the war, they had practically nothing in the way of endoscopic equipment.

This is an interesting work which suggests that most urologists have been a bit too conservative in treating badly injured or severely strictured urethras.

ANNOUNCEMENT

The Fifteenth Annual Assembly of the United States Chapter of the International College of Surgeons will be held in Cleveland, Ohio, October 31 to November 3, with headquarters at the Cleveland Hotel.

Surgical clinics will be held in several Cleveland hospitals on Monday, October 30. All scientific sessions will be held at the Cleveland Public Auditorium 9 A.M. to 5 P.M. Tuesday through Friday. An excellent program has been arranged, at which time some of the most prominent surgeons of America, and some foreign speakers, will discuss the current contemporary surgical scene.

Through the courtesy of Smith, Kline, & French Laboratories, a colored television program of surgical procedures, originating from the St. Vincent's Charity Hospital, Cleveland, will be shown daily in the auditorium from 9 A.M. to 1 P.M. Motion pictures will also be presented each day depicting many of the recent advances in surgery and surgical technique.

One of the highlights of the meeting will be the annual banquet at the Statler Hotel on Thursday evening when Dr. Frank Lahey of Boston will talk on "Some of the Recent Advances in Surgery." Dr. Elmer Henderson, President of the American Medical Association, will deliver an address on "The Importance of International Cooperation in Surgery."

Reservations may be secured by writing to the Committee on Hotels, International College of Surgeons, 511 Terminal Tower, Cleveland 13, Ohio. Preliminary programs may be obtained from the central office, 1516 Lake Shore Drive, Chicago 10, Ill.